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Original Communications

VARIATIONS IN THE CONCENTRATION OF ASCORBIC ACID IN THE PLASMA OF THE NEWBORN INFANT

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IN A PREVIOUS communication[1] it was shown that the concentration of ascorbic acid in the plasma of the newborn infant diminished by a significant amount after the infant had been on a scorbutogenic diet for only a short period of time. The purpose of the present paper is to present further evidence of the rapidity of response of the plasma concentration to changes in the dietary supply of ascorbic acid.

Van Eekelen,[2] Heinemann,[3] and van Wersch[4] have followed the whole blood ascorbic acid concentrations in normal adults who had been "saturated" by means of orally administered ascorbic acid. They found relatively long periods of depletion necessary for the ascorbic acid concentrations to fall from the high value at saturation to low levels. In one case, six weeks were required to establish a drop from 1.7 to 0.3 mg. per cent. The remaining cases were followed for shorter periods. In one, the blood ascorbic acid went from 1.2 to 0.8 mg. per cent in nine days; in another, from 1.4 to 0.8 mg. per cent in nineteen days; in the third, from 1.0 to 0.3 mg. per cent in twenty-one days; and in the fourth, from 1.8 to 0.6 mg. per cent in fourteen days. Similar studies on infants have not been reported.

Because the only clearly demonstrated function of ascorbic acid is in the formation of mesodermal intercellular substance,[5] and because the newborn infant is forming new mesodermal tissue more rapidly than the adult, it seemed of especial interest to follow the course of the plasma ascorbic acid concentration in newborn infants under different conditions of ascorbic acid intake.

MATERIAL AND METHODS

The infants studied were all full-term, normal infants. They received routine ward care during the experimental period. So far as feeding was concerned, this consisted in nursing at the breast every four hours, except in a few instances where oligogalactia made a three-hour interval

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advisable. In certain cases artificial feedings were necessary. These, whether for complementary or for complete feedings, were composed of cow's milk (2 per cent or 4 per cent) 12 oz., water 5 oz., and karo 1 oz. These mixtures were twice pasteurized, and they contained negligible amounts of ascorbic acid. All the mothers who were nursing infants in the experimental group received the routine house diet. This has been evaluated by Ingalls, Draper, and Teel[6] as containing less than 20 mg. of ascorbic acid daily. Some of the nursing mothers were given in addition daily doses of ascorbic acid during the two-week post-partum period.* Six patients received 600 mg. daily and fourteen received 300 mg. daily in divided doses.

The ascorbic acid concentrations of the infants' blood plasmas were determined at intervals during the experimental period by the micro procedure of Mindlin and Butler.[7] In some cases the ascorbic acid content of the mothers' plasmas were determined by the method of Pijoan and Klemperer,[8] and of the mothers' milk by a modification of the method of Seelig and King.[9]

RESULTS

The concentration of ascorbic acid is considerably higher in the plasma of the newborn infant than in the plasma of the mother. Table I gives the values for thirty infants and mothers within twenty-four hours after birth. The averages are 1.16 and 0.42 mg. per cent, respectively. In no instance is the concentration in the infant less than, or equal to, the concentration in the mother; nor is the infantile concentration in this series ever below the value considered optimal for older individuals, although the majority of the mothers do fall below this level. This relationship is minimized rather than magnified by the error which may possibly be introduced into the determination by the use of potassium cyanide.[10] The greater the concentration in the maternal plasma, the greater is the absolute difference between maternal and infant values, but the smaller is the relative difference between the two. This is in agreement with the findings of Braestrup;[11] Teel, Burke, and Draper;[12] Manahan and Eastman;[13] and Snelling and Jackson.[14]

The high concentration of ascorbic acid in the plasma of the infant at birth is not long maintained. In Table I there can be seen a tendency for the difference between maternal and infant values to be less the longer the time between birth and the collection of the sample. Table II presents the values in fifteen infants shortly after birth, and again after an interval of 48 or 72 hours. The average of the initial determinations is 1.22 mg. per cent, after 48 hours it is 0.74 mg. per cent, and after 72 hours it is 0.67 mg. per cent. During this period, these infants were nursed at the breast. However, lactation does not become established until the third or fourth post-partum day, so that they actually received little nutrient material, especially ascorbic acid. They had the

*The ascorbic acid was supplied by Merck and Company, Rahway, New Jersey.

TABLE I

CONCENTRATION OF ASCORBIC ACID IN PLASMA OF INFANTS AND MOTHERS WITHIN TWENTY-FOUR HOURS OF THE BIRTH

SUBJECT	HR. POST PARTUM	PLASMA ASCORBIC ACID (MG. %)		DIFFERENCE
		INFANT	MOTHER	
Be	1	1.1	0.2	0.9
Th	1	1.9	0.6	1.3
DeM	2	2.3	1.0	1.3
Sc	3	2.0	0.5	1.5
Mo	4	1.5	0.7	0.8
Ja	5	1.2	0.4	0.8
Lu	6	1.9	0.8	0.9
Yo	6	0.8	0.4	0.4
Ha	7	1.5	0.7	0.8
Ca	8	0.6	0.2	0.4
Jo	8	0.6	0.2	0.4
Ei	9	1.4	0.4	1.0
Ea	10	0.8	0.2	0.6
Su	10	1.7	0.5	1.2
Hr	11	0.6	0.2	0.4
O'C	11	0.6	0.1	0.5
Wa	12	0.6	0.2	0.4
Ho	14	0.8	0.1	0.7
Ec	14	1.2	0.6	0.6
Mu	15	0.5	0.3	0.2
Hi	16	0.8	0.3	0.5
McD	18	1.3	0.4	0.9
Sa	19	0.8	0.3	0.5
Wo	19	0.8	0.2	0.6
Ma	20	1.0	0.5	0.5
Ro	22	1.0	0.6	0.4
Fa	22	1.3	0.6	0.7
Or	23	0.8	0.3	0.5
Pr	24	1.4	0.5	0.9
Sw	24	1.7	0.5	1.2
Average		1.16	0.42	0.74

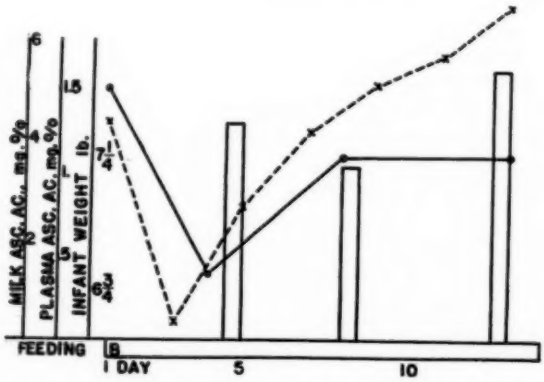
TABLE II

FALL IN PLASMA ASCORBIC ACID CONCENTRATION IN THE FIRST DAYS OF LIFE

SUBJECT	PLASMA ASCORBIC ACID CONCENTRATION (MG. %)				WEIGHT LOSS (OZ.)
	AT BIRTH	48 HR. LATER	72 HR. LATER	DIFFERENCE	
Be	1.1	0.4		0.7	8½
Sc	2.0	1.2		0.8	11
Lu	1.9	0.5		1.4	13
Ei	1.4	0.9		0.5	10½
Wo	0.8	0.7		0.1	12
Mo	1.5		0.4	1.1	12
Ea	0.8		0.6	0.2	16
Ho	0.8		0.4	0.4	7½
Fa	1.3		0.8	0.5	11
Su	1.7		0.9	0.8	7½
Or	0.8		0.6	0.2	11
DiG	1.3		1.0	0.3	8¼
Mu	1.5		1.0	0.5	10½
Me	1.0		0.6	0.4	11
Sa	0.8		0.4	0.4	9½
Average	1.22	0.74	0.67		

customary weight loss from the first to the third day, ranging from 7½ to 16 oz. There is no correlation in this group between the amount of weight lost and the amount or the degree of fall in the plasma ascorbic acid. The findings of Fleming and Sanford[15] of identical concentrations in maternal and infant plasma are undoubtedly explained by the fact that these workers did their determinations on the second day of life. By this time there had been a significant fall in the ascorbic acid concentration of the infants' plasmas.

The subsequent course of the ascorbic acid content of the plasma apparently depends upon the diet of the infant. When lactation becomes established and an adequate supply of breast milk rich in ascorbic acid is available, the initial fall is rapidly overcome. The resulting rise is seldom to the initial concentration. Chart 1 shows the typical course in an infant who received *satisfactory* breast feeding. The mother was in a good state of ascorbic acid nutrition, as indicated by her initial plasma concentration of 0.7 mg. per cent, and by milk values of 4.0 and 5.4 mg. per cent. The infant received an adequate amount of milk, for he gained weight well. After the initial fall from 1.4 mg. per cent to 0.4 mg. per cent, the plasma ascorbic acid had risen by the eighth day to 1.1 mg. per cent, and it was the same on the fourteenth day.



Charts 1 to 8.—Variations in plasma ascorbic acid concentration related to infant's weight, feeding history and ascorbic acid content of the milk. The same symbols are used in all the charts.
o——o Ascorbic acid concentration in infant plasma.
x----x Infant's weight.
Ascorbic acid concentration of breast milk is represented by the vertical unshaded column.
Chart 1 is that of a breast-fed infant, maternal plasma ascorbic acid at delivery 0.7 mg. per cent.
B, breast feeding only.

The breast-fed infant whose ascorbic acid supply is less abundant despite adequate nursing according to ordinary criteria is represented in Chart 2. The concentration of ascorbic acid in the mother's plasma was only 0.1 mg. per cent at delivery, and its concentration in the milk varied between 1.9 and 2.8 mg. per cent. Shortly after birth, the infant's plasma

value was 0.8 mg. per cent; on the fourth day it was 0.4 mg. per cent, by the thirteenth day it had risen to 0.7 mg. per cent. This infant also gained weight normally.

If ascorbic acid is administered freely during lactation its concentration in the milk is increased.[9] Chart 3 shows the result in the infant of such a procedure. At delivery the mother had 0.6 mg. per cent of ascorbic acid in the plasma. For two weeks post partum she was given

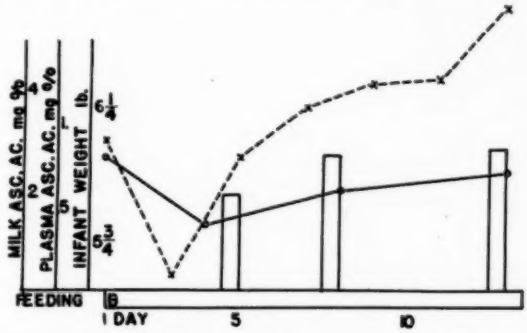


Chart 2.—Breast-fed infant, maternal plasma ascorbic acid at delivery 0.1 mg. per cent.
B, breast feeding only.
Symbols same as in Chart 1.

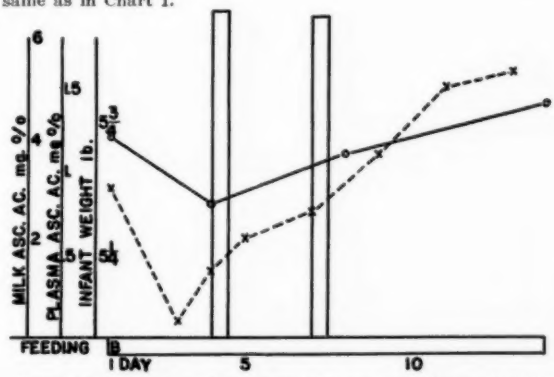


Chart 3.—Breast-fed infant, mother given 600 mg. ascorbic acid daily. Maternal plasma ascorbic acid at delivery 0.6 mg. per cent, on thirteenth day 1.7 mg. per cent.
B, breast feeding only.
Symbols same as in Chart 1.

600 mg. of ascorbic acid daily in divided doses. The plasma concentration of ascorbic acid rose to 1.7 mg. per cent, and her milk contained between 5.0 and 6.5 mg. per cent. The infant at birth had a plasma value of 1.2 mg. per cent; on the fourth day it was 0.8 mg. per cent. It is probable that this does not represent the lowest level in this case, for a substantial gain in weight had occurred between the third and fourth days, and at this time the milk contained 6.4 mg. per cent of ascorbic acid, so that the period of depletion had ended. At two weeks of age, this infant had 1.4 mg. per cent of ascorbic acid in the plasma.

Seven infants were satisfactorily nursed at the breast for the first two weeks of life by mothers who received 300 or 600 mg. of ascorbic acid daily. The ascorbic acid concentrations in the plasmas of these infants averaged 1.4 mg. per cent, with a range from 1.1 to 1.6 mg. per cent (Table III). This may be compared with the average of 1.0 mg. per cent and range from 0.5 to 1.6 mg. per cent previously reported in a similar group whose mothers had received no supplement of ascorbic acid.[1] The latter individuals represent the average patient seen in this clinic.

TABLE III

PLASMA ASCORBIC ACID CONCENTRATION OF 2-WEEK-OLD INFANTS (BREAST-FED) WHOSE MOTHERS RECEIVED ASCORBIC ACID DAILY POST PARTUM

SUBJECT	DAILY ASCORBIC ACID (MG.)	PLASMA ASCORBIC ACID (MG. %)
Fa	600	1.6
Yo	600	1.5
Ec	600	1.4
Ei	600	1.1
Gr	300	1.4
Mu	300	1.4
Ja	300	1.3
	Average	1.4

If the infant's daily supply of ascorbic acid is modified, the change is very quickly reflected in the plasma. This is illustrated in the remaining charts. In Charts 4 and 5 the mothers were given 300 mg. of ascorbic acid daily so that their milks contained it in high concentration. With satisfactory nursing, the plasma ascorbic acid concentrations of the infants would have been well over 1.0 mg. per cent at two weeks of age. In Chart 4 the infant failed to gain, and at discharge was still well below birth weight. His plasma ascorbic acid concentration fell to a low normal the day after complementary feedings were given, and thereafter remained constant, as did his weight. The infant in Chart 5 gained weight well during the first week. But this weight gain came largely from the complementary feedings, and the plasma ascorbic acid on the eighth day was 0.6 mg. per cent. Thereafter, the breast milk increased in amount, so that complementary feeding was not necessary, and at discharge the infant's plasma contained 0.8 mg. per cent of ascorbic acid. Similarly in Chart 6, the mother in question was in a poor state of ascorbic acid nutrition and received no ascorbic acid supplement, and oligogalactia and complementary artificial feedings were accompanied by a fall in the ascorbic acid content of the infant's plasma; but the development of a more abundant supply of breast milk, resulting in a substantial gain in weight by the infant without the benefit of artificial feeding, was accompanied by a marked rise in the ascorbic acid concentration of the plasma in spite of the relatively low concentration in the mother's milk.

Withdrawal of all ascorbic acid from the diet of the newborn infant results in low plasma concentrations in a short time. The infant represented in Chart 7 was artificially fed from birth and gained weight well. He showed a progressive fall in plasma ascorbic acid concentration from an initial value of 1.7 mg. per cent shortly after birth to

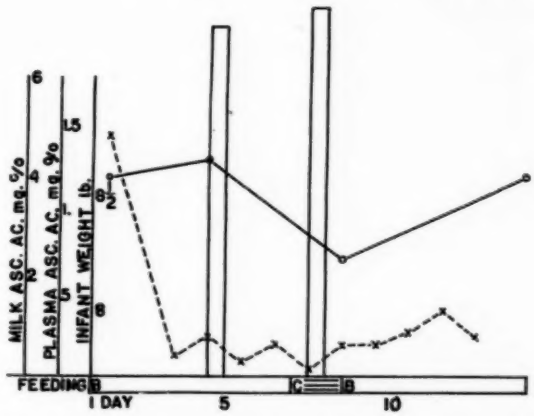


Chart 4.—Breast-fed infant; complementary feeding for 2 days; failure to gain. Mother given 300 mg. ascorbic acid daily. Maternal plasma ascorbic acid at delivery 0.4 mg. per cent, on seventh day 1.2 mg. per cent.
B, breast feeding only; *C*, breast feeding and complementary artificial feeding.
Symbols same as in Chart 1.

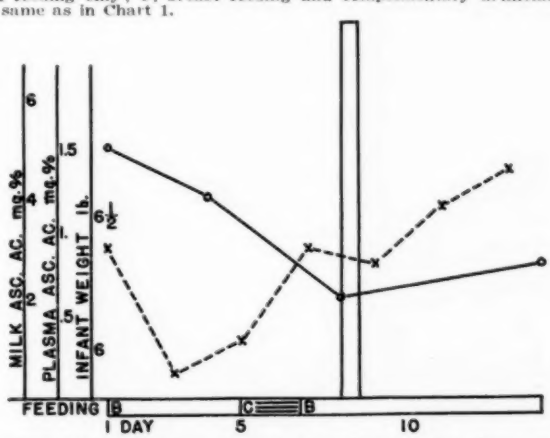


Chart 5.—Breast-fed infant, complementary feeding for 2½ days; mother given 300 mg. ascorbic acid daily. Maternal plasma ascorbic acid at delivery 0.6 mg. per cent, on seventh day 1.4 mg. per cent.
B, breast feeding only; *C*, breast feeding and complementary artificial feeding.
Symbols same as in Chart 1.

0.2 mg. per cent at thirteen days. In Chart 8 the infant had a lower initial concentration, 0.8 mg. per cent, and he received a small amount of breast milk during the first five days together with complementary feedings. On the sixth day breast feeding was omitted entirely, and

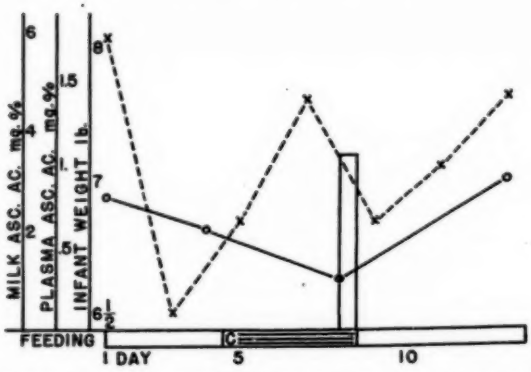


Chart 6.—Breast-fed infant; complementary feeding for 5 days; maternal plasma ascorbic acid at delivery 0.2 mg. per cent.
B, breast feeding only; *C*, breast feeding and complemenary artificial feeding.
Symbols same as in Chart 1.

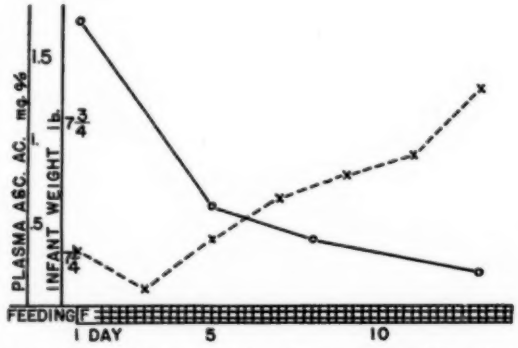


Chart 7.—Artificially fed infant. Maternal plasma ascorbic acid at delivery 0.5 mg. per cent.
F, artificial feeding only.
Symbols same as in Chart 1.

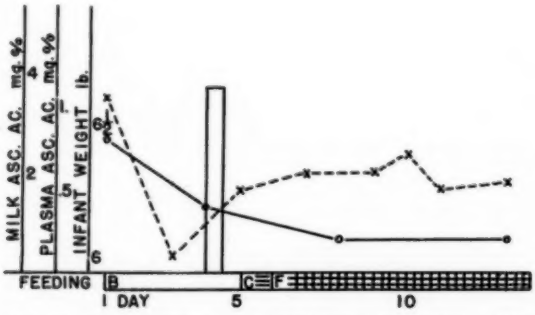


Chart 8.—Breast, complementary and artificially fed infant. Maternal plasma ascorbic acid at delivery 0.2 mg. per cent.
B, breast feeding only; *C*, breast feeding and complementary artificial feeding; *F*, artificial feeding only.
Symbols same as in Chart 1.

by the eighth day the plasma ascorbic acid concentration was 0.2 mg. per cent, where it remained for the following six days.*

DISCUSSION

The data presented indicate a very close relationship between the ascorbic acid content of the diet and of the blood plasma. The infant at birth apparently has a very high ascorbic acid endowment, if the indophenol-reducing substance of the plasma is indeed ascorbic acid, for the concentration is in the zone found with "saturation" in adults. A short period of ascorbic acid starvation results in a prompt diminution in its plasma concentration. However, this does not necessarily signify depletion of the tissues to a similar extent. The prompt rise in plasma ascorbic acid concentration with the resumption of only a moderate amount of dietary ascorbic acid, as in Chart 6, shows that no marked depletion of the tissues could have occurred in that interval. In clinical scurvy it has been demonstrated[16] that the plasma ascorbic acid concentration does not rise to an optimal level for some time after the administration of large amounts of ascorbic acid had begun.

In continued ascorbic acid starvation, the organism passes through three stages. First there is a period of ascorbic acid depletion which is manifest only by diminishing concentrations of ascorbic acid in the various tissues of the body. This cannot truly be called ascorbic acid deficiency, inasmuch as there is no known impairment of physiologic processes. The second stage is a period of asymptomatic scurvy in which there is histologic evidence of deviation from the normal. Hamil, Reynolds, Poole, and Macy[17] have observed its development and spontaneous disappearance in infants receiving 10 mg. of ascorbic acid daily. The only associated findings were slight flattening of the growth and weight curves during the interval when the minimal x-ray changes were present. The third stage is the period of clinical scurvy with its gross pathologic changes.

The concentration of ascorbic acid in the plasma, as determined by existing methods, is not an index of the state of the organism with respect to the three stages of ascorbic acid depletion (or saturation), at least in the newborn infant. Changes in plasma ascorbic acid concentration occur rapidly, in response to small changes in dietary ascorbic acid. After two weeks of a scorbutogenic diet the infant's plasma contains only 0.2 mg. per cent of ascorbic acid; yet clinical scurvy does not ordinarily occur until the fourth or fifth month, and histologic scurvy is rare before three months of age. Ingalls[18] has reported asymptomatic scurvy in infants of 26, 32, and 57 days of age who died of infections. These infants had received insignificant amounts of ascorbic acid. Moreover, they all had severe infections, with concomitant increase in their

*These results are not entirely comparable with those of the Utrecht school[2, 3, 4] previously discussed, where the ascorbic acid concentration of whole blood was determined.

ascorbic acid requirements.[19] Hamil and co-workers[17] have detected asymptomatic scurvy by early x-ray changes in infants of 61, 98, and 176 days of age who were given no ascorbic acid except that contained in the evaporated milk of their formulas (0.2 mg. per ounce). These infants also suffered mild infections. In both groups the plasma ascorbic acid concentration must have been well below 0.2 mg. per cent for a considerable interval before the development of the histologic or x-ray evidence of asymptomatic scurvy.

SUMMARY

1. The concentration of ascorbic acid in the plasma of the newborn infant at birth is greater than in the plasma of the mother.

2. The concentration of ascorbic acid in the plasma of the newborn infant during the first two weeks of life varies directly and promptly with changes in the ascorbic acid content of the diet.

3. The concentration of ascorbic acid in the plasma of the newborn infant falls rapidly to low levels in ascorbic acid starvation and is not a reliable index as to the degree of asymptomatic scurvy which may be present.

I wish to thank Dr. A. M. Butler for his continued interest and helpful suggestions during the course of this work.

ADDENDUM.—Since this was written, Braestrup[20] has published data which are substantially in agreement with those herein reported.

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VITAMIN A STATUS OF CHILDREN AS DETERMINED BY DARK ADAPTATION

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THE ability of the eye to adapt to darkness is due to the regeneration of visual violet in the cones and of visual purple in the rods of the retina.[1, 2] The regeneration of these retinal pigments, however, is dependent upon the presence of vitamin A.[3] When there is a diminution in the quantity of vitamin A in the retina, there is an insufficient formation of visual violet and visual purple, and, as a result, poor dark adaptation, or night blindness, develops.

Within the past few years several instruments have been devised for testing dark adaptation.[4] As a result of their use, a number of persons, although appearing normal in every way, were found to have poor dark adaptation which returned to normal following the administration of adequate amounts of vitamin A. Thus, poor dark adaptation is a manifestation of very mild vitamin A deficiency and, in the light of our present knowledge, represents the most outstanding sign of subclinical vitamin A deficiency.

The course of dark adaptation in a person placed on a diet almost devoid of vitamin A is illustrated in Chart 1. The data are those of Hecht and Mandelbaum,[5] and the curves represent the course of dark adaptation at various stages of vitamin A deficiency. The horizontal axis indicates the time in the dark, whereas the vertical axis represents the light threshold, i.e., the minimum intensity of light observed by the subject. The threshold is expressed in micromicrolamberts, the logarithm of this photometric unit being employed. Thus, a value of 3 represents a light intensity of 1,000 micromicrolamberts; a value of 4, 10,000 micromicrolamberts, etc. Following an exposure to a bright light (1,500 millilamberts) for three minutes, measurements of the light threshold are made at intervals of from one to four minutes.

It has been demonstrated that the first phase of dark adaptation after exposure to a bright light is a function of the cones of the retina, whereas the second and longer phase is the result of rod function.[6] It will be noted in Chart 1 that, after twenty-five minutes in the dark, the light threshold reaches a relatively constant value, and the person is then completely dark adapted. The minimum intensity of light observed during the period of complete dark adaptation represents the final rod threshold. The chart clearly illustrates that a diet deficient in vitamin A brings about an elevation of the final rod

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threshold, and, to a lesser extent, of the final cone threshold. Thus, after the subject was on a diet almost devoid of vitamin A for thirty-five days, the final rod threshold was raised 2 log units (100 times), and the final cone threshold, 1 log unit (10 times). It should also be noted that the rate of dark adaptation is not influenced as a result of a diet low in vitamin A, the final rod threshold being reached as quickly on a vitamin-A-deficient diet as on a normal diet. Wald, Jeghers, and Arminio[7] and Booher, Callison, and Hewston[8] have also found that an inadequate intake of vitamin A causes a rise in the final rod and cone thresholds, but has no effect on the rate of dark adaptation.*

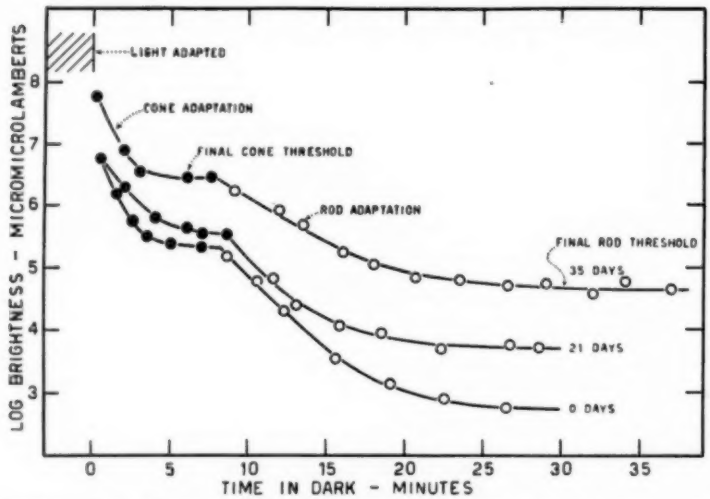

Chart 1.—The influence of a diet almost devoid of vitamin A on the course of dark adaptation (after the data of Hecht and Mandelbaum). The filled circles represent cone threshold measurements, whereas the unfilled circles represent rod threshold measurements. The number of days that the subject had been on the vitamin-A-deficient diet is recorded at the end of each curve.

It is evident, therefore, that measurements of the final rod threshold alone, will suffice for the detection of vitamin A deficiency in persons receiving an insufficient quantity of vitamin A in their diets. To determine the final rod threshold, previous exposure to a bright light is not required. The subject is placed in a dark room and in a period of twenty-five minutes is completely dark adapted. The final rod threshold is then obtained by measuring the minimum intensity of light observed

*In this connection it may be added that, in patients having cirrhosis of the liver, Haig, Hecht, and Patek[9] found that there was a delay in dark adaptation, the final rod threshold being reached in forty to sixty minutes, and that, with the administration of large quantities of vitamin A to these persons, the rate of dark adaptation returned to normal. It has been shown, however, that the delay in adaptation in patients suffering from cirrhosis of the liver is not due to an inadequate intake of vitamin A, but is probably the result of a disturbance in the intermediary metabolism of vitamin A.[10]

by the subject. If the threshold is found to be higher than that of normal persons, it may be assumed that a state of vitamin A deficiency exists, provided, of course, that there is no organic lesion in the eye to account for the high threshold. To establish the diagnosis of vitamin A deficiency, however, a therapeutic test should be carried out, namely, the administration of large quantities of vitamin A by mouth, and the return of the threshold to a normal value should result. If there is any indication of faulty absorption of the vitamin, the therapeutic test should consist of the administration of vitamin A parenterally.

In a previous communication[11] we have recorded our observations on the final rod threshold of infants placed on diets containing varying quantities of vitamin A. For that investigation we devised a portable adaptometer which proved to be most satisfactory in obtaining reliable data on the visual threshold of infants in the dark.[12] Three infants receiving a diet almost devoid of vitamin A developed high threshold values. Thirty thousand to fifty thousand units of vitamin A were given to two of these infants, and the threshold returned to normal in forty and sixty-five minutes, respectively. When minimal quantities of vitamin A (60-120 units) were added daily to the diet, the threshold returned to normal in about one month.

We found that, as judged by dark adaptation, the minimum requirement of infants is approximately 18 to 20 international units of vitamin A per kilogram of body weight. This unitage represents an amount of vitamin A which is about one-twelfth to one-fifteenth the vitamin A intake of the average infant. The margin of safety with respect to the vitamin A content of the average diet of infants is therefore very large. It is for this reason that vitamin A deficiency is so uncommonly seen in infants.

The present study was undertaken to determine the frequency with which vitamin A deficiency is encountered in children in New York City. We employed the same apparatus as was devised for our study on infants, and the final threshold was used as an indicator of vitamin A deficiency. The procedure, however, was slightly modified inasmuch as the children were able to inform us as to whether or not they saw the test light. It may be recalled that, in the study on infants, the visual threshold in the dark was determined by ascertaining the minimum intensity of light which elicited a movement of the head in the direction of the light as indicated by a luminous vial attached to the forehead of the infant. The procedure employed for obtaining the final rod threshold in children was as follows:

The child was placed in a dark room, and after thirty minutes the test light was moved at a distance of approximately 10 cm. in front of his eyes through an arc of 180 degrees. The child was asked whether

or not he saw the light and, to make the test objective, was required to state whether the light was on the right or left side of his visual field.* By means of a series of filters placed within the instrument, the intensity of the light could be varied, and the minimum intensity visible to the child was regarded as the final rod threshold. The micromicrolambert was the photometric unit used (1 micromicrolambert = 1 foot candle $\times 1.076 \times 10^{-9}$), and, for convenience, the threshold values obtained were expressed in logarithms.

Excellent cooperation was obtained in most of the children on whom the tests were conducted. The procedure was so simple that the children were able to follow directions without any difficulty. That there was no learning factor is indicated by the fact that subsequent tests did not yield lower threshold values than those of the original tests. Some children attempted to guess the position of the test light, but this was readily detected by keeping the light on one side of the visual field for some time instead of quickly alternating its position. Occasionally, we would turn out the light and then ask the child whether or not he saw it in order to ascertain the reliability of the child's responses.

Dark adaptation tests were carried out on sixteen private patients, aged 6 to 12 years. These children were normal and came from fairly well-to-do homes. The results of the dark adaptation tests in these children revealed threshold values ranging from 1.6 to 2.5 (log micromicrolamberts). Repeated tests disclosed that, in most instances, the same values were obtained, whereas in some children there was a variation of only .3 log unit. This variation represents approximately .2 per cent of the total range of rod adaptation.†

TABLE I

EFFECT OF THE DAILY ADMINISTRATION OF 25,000 INTERNATIONAL UNITS OF VITAMIN A FOR A PERIOD OF SIX WEEKS UPON THE FINAL (ROD) THRESHOLDS OF NORMAL CHILDREN

NAME	AGE	THRESHOLDS PRIOR TO VITAMIN A THERAPY	THRESHOLDS AFTER VITAMIN A THERAPY
D. L.	7	2.2	2.2
M. W.	7	2.2	2.2
M. L.	7	1.9	1.9
S. J.	6	1.9	2.2
S. Q.	6	2.2	2.2
A. L.	8	2.5	2.5
N. M.	10	1.9	2.2
C. U.	7	2.5	2.5*

*Threshold was measured after child had been receiving 25,000 units of vitamin A for three months.

*We have had occasion to carry out dark adaptation tests in two young children, 3 and 5 years of age, respectively, who could not distinguish between right and left. A luminous vial was fastened by adhesive plaster to the index finger, and the child was asked to point to the position of the test light. With this technique we were able to obtain threshold values in these two children.

†It has been shown by Hecht, Haig, and Chase[17] that the total range of rod adaptation covers three log units (1,000:1). Thus, .3 log units (2:1), is one-five-hundredth of the total range, or .2 per cent.

The question was raised whether the administration of large quantities of vitamin A daily could lower the final rod threshold in normal children. To obtain information on this point, eight normal children were given 25,000 units of vitamin A daily in the form of halibut-liver oil* for a period of six weeks. In Table I the thresholds prior to and following the administration of those large quantities of vitamin A are given. It will be noted that, despite these large doses of vitamin A, no change in the theshold resulted. This experiment, furthermore, established the fact that the range, 1.6 to 2.5, represents the normal range in children under the conditions of our experiment.

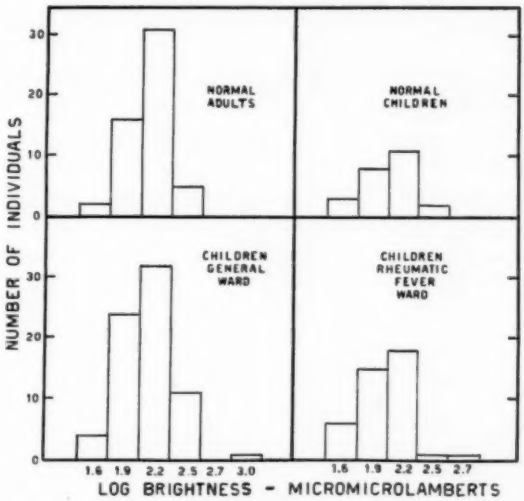

Chart 2.—The distribution of the final rod thresholds of normal children and adults, as well as of children on the general and rheumatic fever wards of Bellevue Hospital.

A glance at Chart 2 will reveal that the range of threshold values obtained in the twenty-four normal children was the same as that noted in fifty-four normal adults examined with the same apparatus under similar conditions. A slightly higher incidence of 1.6 values was obtained in the children as compared with the adults. The mean value, however, was 2.1 in the children and 2.0 in the adults, and the mode (the most frequent value) was the same in both groups, namely 2.2.† It should be added that the distribution of the thresholds was almost exactly the same in both sexes.

*Halibut liver oil was supplied through the courtesy of Mead Johnson & Company.

†These thresholds are approximately 1 log unit lower than those previously reported in adults with the Hecht-Shlaer instrument. The reasons for this difference in thresholds are as follows:

1. With our procedure we measure the threshold of the most sensitive portion of the retina, whereas the thresholds obtained with the Hecht-Shlaer apparatus are those of a less sensitive area, namely, 7 degrees nasal to the fovea.
2. The test in our apparatus subtends an angle on the retina of 7 degrees as compared with the 3-degree angle in the Hecht-Shlaer procedure.
3. The duration of the exposure to the test light is prolonged in our procedure as compared with a short exposure of one-fifth second with the Hecht-Shlaer apparatus.

Having established the normal range of the final rod threshold in children, we then carried out dark adaptation tests on seventy-two children who came from one of the poorest sections in New York City. Sixty-three of these children were patients on the general wards of Bellevue Hospital, and nine were seen in the Outpatient Department. More than one-half of these children came from families on home relief, and it is therefore apparent that, if vitamin A deficiency is at all common among children, it would certainly be manifest in this group. Since most of the children admitted to the hospital were suffering from an acute febrile disorder, a study of this kind would also give information as to the effect of fever and toxemia upon the vitamin A status of children. It is conceivable that children who, prior to their illness, might have been on the borderline of vitamin A deficiency would show, as a result of their illness, evidences of vitamin A deficiency.

Of the sixty-three children admitted to the general wards, fourteen were suffering from pneumonia, and tests were carried out usually as soon as the temperature returned to normal. In several instances, however, we determined the final rod threshold during the febrile state. Children having no febrile disease were usually tested within 48 hours after entrance to the hospital. In addition to acute respiratory diseases, the following conditions were included in this group of children: bronchiectasis, lung abscess, Hodgkin's disease, diabetes, renal calculi, malformation of the ureter, sickle cell anemia, dysentery, hemophilia, vaginitis, asthma, and malnutrition.*

The results of these tests may be noted in Chart 2. It will be observed that the threshold values were normal in all but one instance. Thus, seventy-one of seventy-two children had values ranging from 1.6 to 2.5, the mean being 2.1 and the mode 2.2. One child, aged 9 years, had an abnormally high final rod threshold of 3.0.

The child having the high threshold had been admitted to the hospital because of abdominal pain and was placed on a rigorous diet which was low in vitamin A. He was tested after he had been on this diet for two weeks, and the threshold was found to be 3.0. Repeated tests, within a period of sixteen days, gave the same value. Two and one-half cubic centimeters of oleum percomorphum (approximately 120,000 international units of vitamin A) were given, and, as may be seen in Chart 3, the threshold dropped to 1.9 in thirty-five minutes. The effect of this enormous amount of vitamin A lasted for twenty days, at the end of which time the threshold had again risen to 3.0. A comparable

*Since this paper was submitted, we have had occasion to carry out dark adaptation tests on two children having marked hyperkeratosis of the upper and lower extremities. In both instances the results of the tests revealed normal values. Vitamin A levels of the blood were also within normal limits. In one child biopsy of the skin did not disclose the histologic changes characteristic of vitamin A deficiency. These cases are of interest because of the opinion held by some physicians that all cases of hyperkeratosis are due to vitamin A deficiency.

dose of the provitamin, carotene, was then given to determine whether the threshold would drop as quickly following the administration of the precursor of the vitamin as it was seen to do following the administration of the oily preparation containing vitamin A. As may be noted in Chart 3, the threshold dropped to a level of 1.9 in thirty-two minutes. The provitamin, therefore, brought about as rapid a response as was noted following the administration of the vitamin itself. The child was then placed on a regular diet, and repeated tests, carried out over a period of several months, have revealed normal threshold values.*

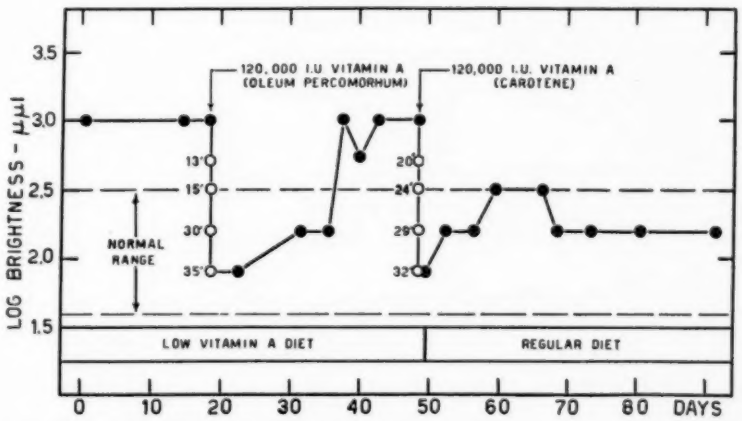

Chart 3.—The effect of an enormous dose of vitamin A and of carotene upon the final rod threshold of a boy who had been receiving a low vitamin A diet. The open circles represent the thresholds following the administration of vitamin A and of carotene. The figures adjacent to the open circles indicate the number of minutes that have elapsed since these preparations were given.

The prompt response following the administration of vitamin A or its precursor, carotene, indicated that the high threshold was due to a lack of vitamin A and that, therefore, this child had a subclinical form of vitamin A deficiency. The question was raised, however, whether a normal final rod threshold, i.e., a value of 1.6 to 2.5, could be rapidly lowered with a single administration of an enormous amount of vitamin A. Accordingly, six children, two with threshold values of 1.9 and four with threshold values of 2.5, were given 200,000 units of vitamin A in the

*During the past year we have seen in private practice two children, aged 7 and 12 years, who had complained, since they were about 5 years of age, of difficulty in seeing at night. Their final thresholds, after complete dark adaptation, were 5.2 and 6.2, respectively. A single administration of 200,000 units of vitamin A, as well as daily doses of 25,000 units for a period of four weeks, had no effect upon these markedly elevated threshold levels. Since there was no evidence of any interference in the absorption of vitamin A, we therefore suspected that the night blindness was due to some cause other than vitamin A deficiency. Ophthalmologic examination was entirely negative. The complete course of dark adaptation was then measured after exposure to a bright light for three minutes, and the results revealed normal cone function, but an absence of rod function. These findings indicate that these children were probably suffering from congenital hemeralopia, which is presumably due to an absence of rods, or of rod function.

form of halibut-liver oil, and the thresholds were again measured one hour later. As may be observed in Table II, no change in the final

TABLE II

FINAL ROD THRESHOLDS OF NORMAL CHILDREN PRIOR TO AND ONE HOUR FOLLOWING THE ADMINISTRATION OF AN ENORMOUS DOSE OF VITAMIN A (200,000 INTERNATIONAL UNITS)

NAME	AGE	THRESHOLDS PRIOR TO ADMINISTRATION OF VITAMIN A	THRESHOLDS ONE HOUR AFTER ADMINISTRATION OF VITAMIN A
J. I.	8	2.5	2.5
J. M.	9½	2.5	2.5
K. D.	9	2.5	2.5
M. L.	7	1.9	1.9
D. L.	7	1.9	2.2
A. R.	9	2.5	2.5

rod threshold resulted from this excessively large dose of vitamin A. This experiment, therefore, established the fact that the threshold value of 3.0 noted in the aforementioned case was the result of vitamin A deficiency. It may be of interest to add that we have also noted a rapid lowering of the final rod threshold in two infants who had high threshold values as a result of diets containing almost no vitamin A. Wald and his co-workers[7] have observed the same phenomenon in adults. On the other hand, Hecht and Mandelbaum[5] were unable to bring about in vitamin-A-deficient subjects an immediate drop in the threshold with the administration of large quantities of vitamin A. Further work must be carried out in order to clarify these divergent findings. For the present it would seem advisable to take the position that, if a rapid lowering of an abnormally high threshold is noted following a single large dose of vitamin A, the diagnosis of vitamin A deficiency is warranted, but, on the other hand, the absence of such response does not rule out the presence of vitamin A deficiency.

Dark adaptation tests were also carried out on forty-two children who were suffering from rheumatic fever. Many of these children had been running a low-grade temperature for several weeks. A good opportunity was, therefore, afforded for determining the effect of a long-standing febrile disease on the vitamin A status of children. It should be added that in twenty-three of these children the diets were not supplemented with vitamin A preparations, whereas sixteen children received one teaspoonful of cod-liver oil daily.

The results of these dark adaptation tests revealed that in forty-one of forty-two rheumatic children the threshold values were normal, 1.6 to 2.5, the mean being 2.0 and the mode, 2.2. In one child the threshold was 2.7, a value slightly higher than that which we have seen in normal children. It is of interest to mention that this child had been receiving two teaspoonfuls of cod-liver oil daily for several weeks. Administration of 200,000 units of vitamin A had no immediate effect upon the threshold. Whether this borderline value of 2.7 was due to the presence

of a very mild degree of vitamin A deficiency cannot be answered. Unfortunately, we were not able to follow up the case and, therefore, could not determine the effect of daily administration of large quantities of vitamin A over a prolonged period. It is probable that in this instance the value of 2.7 represented a normal threshold.

Six children having active tuberculosis were also tested. Diets of four of these children had been supplemented daily with a maltine preparation containing 2.5 gm. of cod-liver oil. Three children had severe forms of tuberculosis, one having tuberculous peritonitis and two having advanced pulmonary tuberculosis. The results of the dark adaptation tests in this group of children revealed normal threshold values. These findings are contrary to those of Getz and his co-workers[18] who, using the biophotometer, reported an incidence of 53 per cent of vitamin A deficiency in ambulatory tuberculous patients despite the fact that the diets had been supplemented with vitamin A in 40 per cent of the deficient subjects.

COMMENT

The results of this investigation revealed that, as judged by dark adaptation, only one child of 144 children showed definite evidence of vitamin A deficiency. When one considers the fact that most of these children came from very poor homes and that, furthermore, many of them had been suffering from a febrile disease, the conclusion seems warranted that vitamin A deficiency is an uncommon disorder in children.

This view differs from that of Jeans and his co-workers,[13] who are of the opinion that vitamin A deficiency is quite prevalent among children. In 1937 they reported that of twenty-three children in an orphanage in Iowa, eight, or 34 per cent, had poor dark adaptation and were, therefore, regarded as suffering from vitamin A deficiency. In a group of thirty-seven school children, nine, or 23 per cent, were found to have poor dark adaptation. It should be mentioned that these investigators employed the biophotometer for measuring dark adaptation. Recent studies by Palmer and Blumberg[14] and by Snelling[15] have demonstrated that the biophotometer, when used in the manner described by Jeans and his associates, is not a satisfactory instrument for obtaining reliable data in children. Moreover, Isaacs, Jung, and Ivy[16] have shown that the statistical error involved in the use of the biophotometer is high, and Heckt and Mandelbaum[5] state: "The biophotometer does not incorporate in its structure and recommended procedure many of the critical specifications for measuring dark adaptation already referred to and fails to link its results with physiologic knowledge."

It seems to us that the unreliability of the results obtained with the biophotometer is due mainly to the fact that too much reliance has been placed upon the measurement obtained twenty seconds after the subject has been in the dark. At this time the threshold is falling

rapidly and it is difficult, especially in children, to obtain a measurement at exactly twenty seconds. This would account for the marked variability of the "20 second" measurements. In our method measurements of the threshold are obtained during complete dark adaptation, at which time the threshold is constant and can therefore be determined without hurry. Furthermore, the values can be checked repeatedly during this phase of dark adaptation.

The minimum vitamin A requirement for children has not yet been ascertained. However, a consideration of the requirements of vitamin A for infants and adults, as well as for experimental animals, throws some light upon the probable requirement for children. Thus, it has been demonstrated that infants require approximately 18 to 20 units of vitamin A per kilogram of body weight for the maintenance of normal dark adaptation, whereas adults, according to Edmund and Clemmesen,[19] require about 20 to 22 units per kilogram of body weight. Booher and her co-workers[8] reported in a recent investigation that the daily intake of vitamin A necessary for normal dark adaptation in five adults varied between 25 and 55 units per kilogram of body weight.

In experiments conducted upon sheep, swine, and cattle, Guilbert and his collaborators[20] found that 6 to 8 micrograms of vitamin A (20 to 27 units) per kilogram of body weight prevented the development of night blindness and that they represent the minimum requirement for these animals. Employing the appearance of cornified epithelial cells in vaginal smears as an indicator of vitamin A deficiency in the rat, Goss and Guilbert[21] report that 18 to 22 units of vitamin A per kilogram of body weight may be regarded as the minimum requirement for the rat. Guilbert and his co-workers are of the opinion that the vitamin A requirement is dependent upon body weight and is approximately the same, per kilogram of body weight, for all mammals. Our observations on infants, as well as those obtained on adults, are, in general, in accord with this hypothesis.

From the foregoing considerations it seems likely that the minimum requirement for vitamin A in children is of the same order of magnitude as the minimum requirement in infants and adults. The average diet of children of from 6 to 12 years of age contains approximately 5000 units of vitamin A. Since children of 6 years weigh about 22 kg., and those of 12 years, 40 kg., the average diet provides about 125 to 250 units of vitamin A per kilogram of body weight for children of this age group. These calculations indicate that the margin of safety with respect to the vitamin A content of the average diet of children is large. The infrequency with which we have observed vitamin A deficiency in children lends support to this view. It would, therefore, seem superfluous to supplement the average diet of children with vitamin-A-containing preparations except in those instances in which a considerable portion of the diet is refused or vomited.

SUMMARY

The purpose of this investigation was to determine the frequency with which vitamin A deficiency is encountered in children. In view of the fact that vitamin A deficiency brings about an elevation in the final rod threshold, i.e., the minimum intensity of light observed by the subject after complete dark adaptation, we made use of the final rod threshold level as a criterion of vitamin A deficiency. Accordingly, the final rod threshold was determined in 144 children ranging in age from 6 to 12 years. Sixteen of these children were private patients, whereas the remainder were observed either in the wards or in the Outpatient Department at Bellevue Hospital. Forty-two children had rheumatic fever, fourteen had pneumonia, six had active tuberculosis, and the remainder were suffering from one of the following conditions: upper respiratory infection, lung abscess, bronchiectasis, Hodgkin's disease, diabetes, renal calculus, malformation of the ureter, malnutrition, sickle cell anemia, dysentery, hemophilia, vaginitis, and asthma.

Dark adaptation tests revealed normal threshold values in all but one instance. The sole exception was in a child who, because of abdominal pain, had been placed on a rigorous diet which was low in vitamin A. Administration of 120,000 units of vitamin A in the form of percomorph-liver oil brought about a fall of the threshold to a normal value in thirty-five minutes. The effect of this enormous dose lasted twenty days, at the end of which time the threshold again reached an abnormally high level. The provitamin, carotene (120,000 units) was then given, and a prompt response was again noted, the threshold returning to normal in thirty-two minutes. This child was then placed on a regular diet, and repeated tests over a period of several months have revealed normal values.

The results of this investigation indicate that vitamin A deficiency, as judged by dark adaptation, is an uncommon disorder in children in New York City.

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NEUROLOGIC SEQUELAE OF PARANATAL* ASPHYXIA

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> AS THE slow onset of anoxaemia advances, the senses and intellect become dulled without the person being aware of it; and if the anoxaemia is suddenly relieved by means of oxygen or ordinary air, the corresponding sudden increase in powers of vision, hearing, etc., is an intense surprise. The power of memory is affected early, and is finally almost annulled, so that persons who have apparently never lost consciousness can nevertheless remember nothing of what has occurred. Powers of sane judgment are much impaired, and anoxaemic persons become subject more or less to irrational fixed ideas, and to uncontrolled emotional outbursts. Muscular co-ordination is also affected, so that a man cannot walk straight or write steadily. With further increase in the anoxaemia, power over the limbs is lost; the legs being first paralyzed, then the arms, and finally the head. The senses are lost one by one, hearing being apparently the last to go.[1]

In the above paragraph from his book *Respiration*, Haldane accurately describes a sequence of symptoms which are familiar to those of us who have had the opportunity of observing patients who have recovered sufficiently from asphyxia for a neurologic examination. Although the symptoms of cerebral anoxemia may have been very alarming, complete recovery of function is apparently possible, provided an adequate supply of air or oxygen is available before prolonged deprivation leaves irreparable tissue damage in its wake. However, if the duration or intensity of the anoxemia is prolonged to the extent of producing sublethal cerebral anoxia, with the resulting cellular destruction, then the clinical pattern described by Haldane may become fixed and irreversible. This fixed pattern of cerebral anoxic organic change is the same, irrespective of the etiology. The commonest presenting symptom of cerebral cell disintegration as a result of destructive anoxia is a deterioration in intellect, evidenced mainly by character change and memory defect. Similar mental deterioration in adults results from asphyxiation from smoke, gaseous anesthesia accidents, inhalation of carbon monoxide, strangulation, or depressed respiration produced by drugs.

The typical mental change associated with an episode of asphyxia was presented by an efficient, 27-year-old female secretary, who was

The support and cooperation provided by the Children's Fund of Michigan are gratefully acknowledged.

*The term *paranatal* has been coined to designate the entire period of fetal life, the period of birth, and the neonatal period within which the results of occurrences during the first two periods may become manifest.

trapped in a closet with four other persons in a fire in 1929. The only survivor, she was unconscious when admitted into the hospital. Following a day of coma, she gradually roused, became wildly delirious, and vomited for two days. When discharged from the hospital one week later, she complained of headache, dizziness, and diminished vision. She had no recollection of any events for several days before or after the fire episode.

This young woman has been examined frequently during the past ten years. Three years elapsed before she could relearn the use of the typewriter; today her typing is poorly done and contains numerous errors. Her sight is seriously impaired; she cannot concentrate on her work; her judgment is faulty; and her memory is unreliable. She is conscious of being "queer"; she is irritable and unreasonable; in fact, there has been a complete change in personality produced by her grave asphyxial exposure in 1929.

With the knowledge that the specialized cells of the brain are identical in function in the infant, child, and adult, it is reasonable to assume that asphyxia produces analogous pathologic changes, possibly more destructive in the younger tissue. Considerable clinical evidence supports the conclusion that the brain tissue of an infant can sustain much less oxygen deprivation than can the adult organ and, therefore, is more readily damaged from this particular cause than is adult cerebral tissue.[2] The clinical diagnosis of such tissue damage is more difficult with the infant since there is no yardstick of previous mentality in evaluation, and the infant (or young child) cannot adequately describe his deficiency. In all deaths from cerebral anoxia, the microscopic lesions are identical, regardless of the cause of the oxygen deficiency in the cellular tissue,[3-5] or age of the subject.[6, 7] The pathologist, with painstaking search, can usually find the typical microscopic degenerative areas in the cerebral cortex and ganglionic structures if the survival period has been even a few hours after occurrence of deficiency in the amount of oxygen compatible with the maintenance of the normal integrity of the cerebral tissue. The microscopic lesions represent various stages of destruction, depending upon the severity and duration of the oxygen deprivation and the survival period following the anoxic insult.

Fig. 1 shows a section* of cortex from a stillborn twin delivered by version and extraction after a twelve-hour labor. The heart sounds of both twins were heard shortly before the spontaneous delivery of the first twin, living; one hour later the second twin was delivered stillborn. All organs showed marked evidence of asphyxia.

If the survival period is some days after severe asphyxia, more advanced lesions may be found. Fig. 2 is a section of tissue from the brain of a 3-day-old infant who was born after a fourteen-hour labor.

*The pathologic diagnoses upon the sections presented in this paper were made by Dr. Gabriel Steiner, Professor of Neurology and Neuropathology, Wayne University College of Medicine.

For twenty-four hours preceding death the child was gasping and cyanotic, despite the administration of carbon dioxide and oxygen. At autopsy, multiple focal hemorrhages were found in the lungs and peritoneum, as well as in the falx and tentorium.

Fig. 3 is a section from the brain stem of an infant who died forty-eight hours following an asphyxial experience similar to those which, unfortunately, are not uncommon in the series of living damaged children under discussion. This baby was seen when 15 hours old because of convulsions and constant twitching of all extremities. The color was good, but the respirations were grunting and chest breathing was absent. All extremities were spastic, and the eyes were held to the right in spasms.

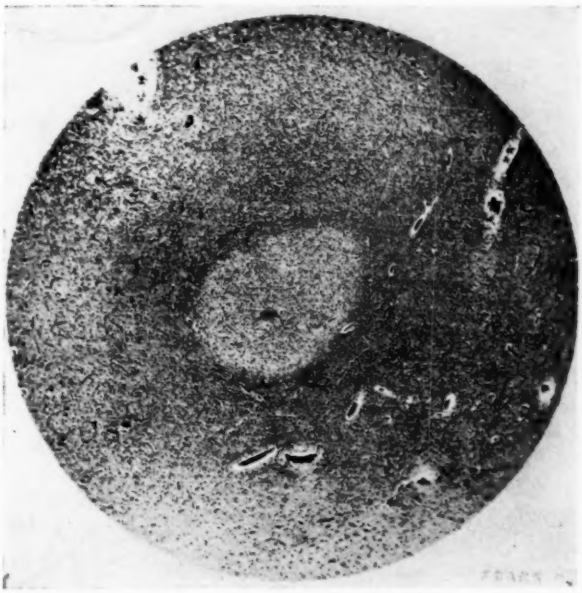

Fig. 1.—Round-shaped area about 0.8 mm. in diameter in the paraventricular gray matter can be grossly detected by its paler aspect in the hematoxylin-eosin staining. Microscopically it is fairly well circumscribed and reveals a more loosened ground substance than that of the surroundings; a beginning degeneration of ganglion cells in this region with densification of cytoplasmic chromatin; disappearance of nuclear membranes or lack of distinction of the entire nuclear portion of the nerve cell, marked only by a dark and diffuse staining (hematoxylin). The glial nuclei are well preserved and no glial reaction is seen, indicating a very early anoxic effect with beginning devastation.

The story was that the child's head had been held back and nitrous oxide given for one-half hour until the arrival of the attending physician. The baby was born spontaneously as soon as perineal pressure was released and anesthesia discontinued.

The appearance was that of asphyxia pallida, and no heart or breath sounds could be heard for fifteen minutes. Then the child began breathing spontaneously after resuscitation. The baby died after

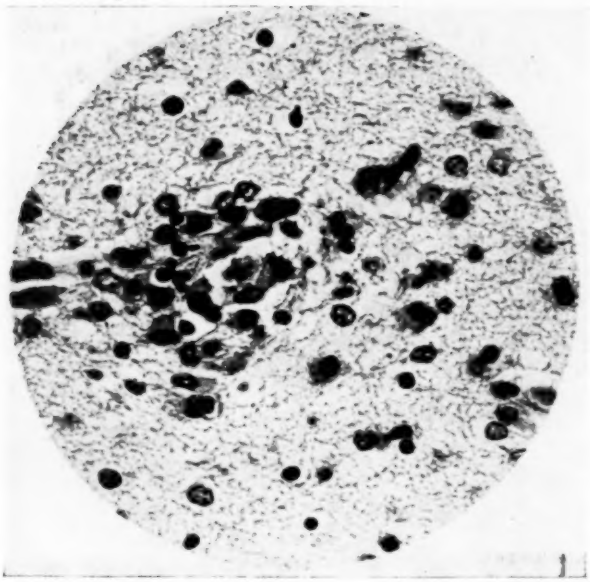

Fig. 2.—Microscopic cortical area of circumscribed glial proliferation consisting of a small number of glial astrocytes which are densely packed together. A few are isolated more peripherally. These astrocytes show increased cytoplasm and numerous small cytoplasmic processes where the glial cells are more singly placed. In spite of the densely packed glial cells, the ground substance is very loose and shows an open meshwork with large empty spaces, but restricted to the circumscribed glial proliferation. This section shows a later stage of anoxic effect than shown in Fig. 1, devastation, and marked glial cytoplasmic reaction.

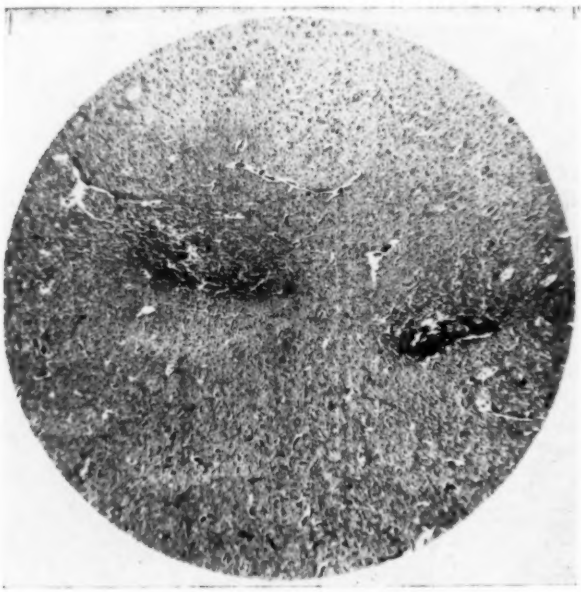

Fig. 3.—Two devastation areas in the medulla associated with extravasation of blood in the region of the tenth nerve nucleus.

forty-eight hours. There was no intracerebral hemorrhage grossly. All organs showed the changes associated with asphyxia.

Dr. Gabriel Steiner has described microscopic sections of the brain which showed two devastation areas associated with asphyxia in the region of the tenth nucleus in the medulla, on the right side, probably responsible for the death of the infant.

More important to the neurologist, however, were the extensive changes secondary to asphyxia in the frontal and motor cortex. Had this child lived, it could be expected to show spasticity, convulsions, or mental retardation, depending upon the location and extent of the lesions.

In order to establish the association between the factor of asphyxia at birth and the degenerative cortical and nuclear lesions believed responsible for the later evidence of brain degeneration in certain of these cases, it is necessary to review briefly certain fundamentally accepted facts relating to the organization and applied physiology of the known areas of the central nervous system. Of all the vital elements necessary to life, oxygen is the most important. The brain cannot dispense with it for more than a few minutes before irreparable damage will ensue. A highly sensitive molecular group of cells in the medulla, the respiratory center, controls the mechanism for vital cerebral oxidation. There is an indispensable interdependence between the fetal, neonatal, and maternal physiology and pathology of cerebral oxidation. Dysfunction (depression) of the respiratory center may be caused by a variety of physical or chemical agents (trauma, hypnotic drugs and anesthetics, or asphyxia). The pathologic result of asphyxia may be either functional or organic tissue changes due to cerebral anoxia, accompanied by clinical neurologic manifestations. Localized areas of anoxic cerebral necrosis are compatible with life. If death ensues, these areas are demonstrable microscopically as foci of neuronal devastation in the cerebral tissue architecture.

Many writers have called attention to the association between birth injury and later fixed brain lesions. These same observers have noted the occurrence of asphyxia at birth in a considerable number of their cases. Doll, Phelps, and Melcher,[8] in a detailed study, listed "deficient animation" at birth in eight of their ten cases of mental deficiency following birth injury in which the pertinent birth data were known. It appears significant, in the author's group of more than 900 children whose brain defect was thought to be related to conditions at birth, that of those for whom reliable birth data were obtainable, 70 per cent were found to have a history of asphyxia, regardless either of the manner of delivery or whether the baby was full term, premature, or a twin. This group of children included those born in the years 1928 through 1939 who were seen with fixed brain lesions as a symptom and about whom the respiratory situation at birth was known. Any

child for whom an inherited defect was suspected or for whom there was a history of postnatal cerebral trauma or infection was excluded from the group. Most of these children, observed at the Children's Hospital of Michigan and in private practice, were referred with convulsions or spasticity by pediatricians or psychiatrists for an opinion as to the advisability of neurosurgical measures or encephalography.

In a careful review of the maternal, prenatal, and birth histories of these neurologically defective children, it was evident that single or combined anoxic factors contributed to the mechanism responsible for the production of asphyxia. In some cases, a carefully recorded history disclosed events occurring during pregnancy which may have been responsible for cerebral cell damage in the fetus; in other cases, the clinical syndrome of the neurologic findings suggested that the devastating cerebral asphyxia came on shortly after the baby was born. The interrelationship between the different type mechanisms by which infant brain tissue may be deprived of oxygen with resultant cell necrosis and later evidence of cerebral dysfunction is schematically shown in Fig. 4. These types have been classified as *anoxic, anemic, stagnant,* and *histotoxic* anoxia.

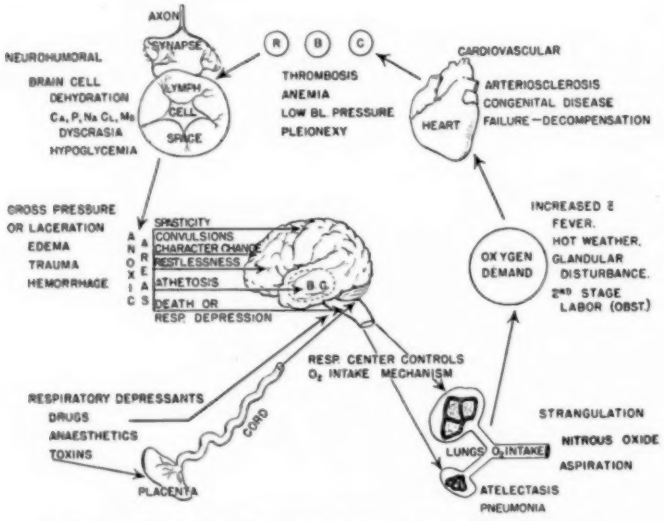

Fig. 4.—The interrelationship of the various types of anoxia.

In *anoxic anoxia* the arterial blood is insufficiently saturated with oxygen.[9] Any type of strangulation occurring in the newborn child (aspiration of mucus, an excessive amount of amniotic fluid in the pulmonary alveoli, or an enlarged thymus compressing the trachea) may produce this type of anoxia. Any sufficiently intense suffocation to which the mother may be subjected during pregnancy (the anoxemia resulting from nitrous oxide asphyxia during the extraction of a tooth,

oxygen want with nitrous oxide during delivery, pneumonia, strangulation from any cause) may act as the contributory factor in shutting off the oxygen supply to the fetus.

Damaging cerebral anoxia may result from increased but unfulfilled oxygen demand due to intrinsic or extrinsic causes. Bronk[10] expresses the opinion that altered respiratory demands of the organism produce like modifications in the properties of the respiratory nerve cells, and therefore the frequency of their rhythm. This *catabolic anoxia* is observed in the mother whose increased temperature (fever) during delivery calls for the inevitable 7 per cent increase in oxygen for every degree of rise until the oxygen demand may reach a point where it can no longer be adequately met because of failure of the respiratory mechanism. Some babies perish during delivery on excessively hot days, apparently from the inability of the altered respiratory center of the mother to meet the increased oxygen demand imposed by the excessive heat; others live but with damaged brains. In those cases in which the mother suffered from hyperthyroidism at the time of delivery, it is thought that the brain lesion in the infant resulted from an unfulfilled oxygen demand imposed on the tissues by the thyrotoxicosis.[11]

Interference with the oxygen supply of the fetus may result from pressure or knotting of the umbilical cord. The tremendous maternal motor excitation in the first and second stages of labor, with the superimposed emotional strain, have been observed[12] to produce requirements 80 per cent greater than the normal metabolic level. Unless an increased demand for oxygen is met, deprivation subjects the fetal brain to an oxygen deficiency which may be of sufficient intensity and duration to leave behind irreversible changes in the brain cells and tissue architecture. Some defective children were observed for whom there was a history of premature separation of the placenta, with severe bleeding, during the latter months of pregnancy. The oxygen deprivation in these cases, while not sufficient to cause the death of the fetus, was apparently severe enough to devitalize some of the fetal cerebral tissue.

In *anemic anoxia* the oxygen *capacity* of the blood is abnormally low.[9] The red blood cells principally, and the blood plasma only slightly, carry the oxygen from the lungs into the brain. A marked reduction in the number of the red blood cells in the circulation will act in producing cerebral anoxia; the transporting agent is reduced. Anemia in the pregnant woman is quite common. Neurologic symptoms as the result of cerebral degeneration secondary to a considerable reduction in the red blood cells of the mother before delivery were shown by a baby 9 months of age, referred with convulsive seizures and unable to support his head. Examination revealed a blind and spastic idiot with convulsive spasms of all extremities recurring at intervals of from two to four minutes. Unable to sit up, he exhibited no interest

whatever in his surroundings. Encephalograms demonstrated extensive, generalized cerebral atrophy, especially pronounced in the frontal lobes (Fig. 5).

Splenic anemia had been diagnosed in the mother ten years previous to the pregnancy involved, her sixth. Her third child had a large head, was mentally retarded, and died of a secondary anemia after four months. During the fourth and fifth pregnancies, an anemia diet and transfusions were given, and the children seem normal. Her physician was not informed of the present pregnancy until the day of delivery. She was given a direct transfusion of 500 c.c. of whole blood and during the transfusion went into labor. An hour after the transfusion her red blood count was 1,200,000.

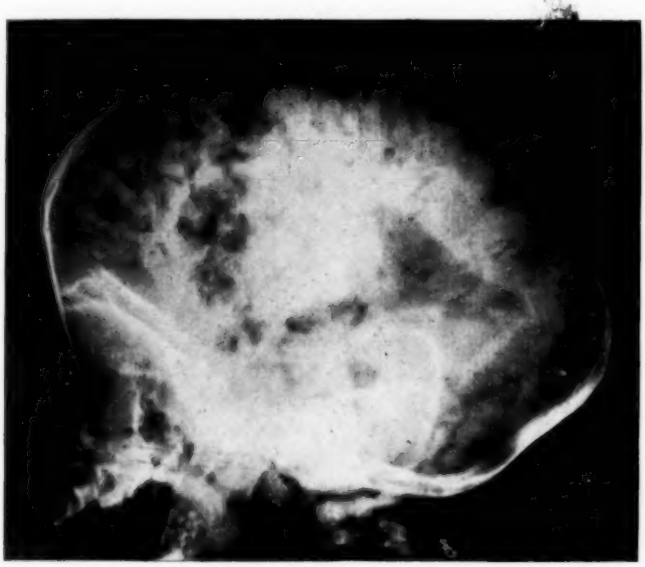

Fig. 5.—Extensive generalized cerebral atrophy in 9-month-old infant.

The child, whose estimated fetal age was eight months, was delivered spontaneously without the use of analgesia and with only light nitrous oxide-oxygen anesthesia at the termination of labor. According to the neonatal record, the baby was cyanotic at birth and recurrently until the fourth day. Three days after delivery, the baby's trunk and extremities became rigid at intervals of a few minutes. The red cell count of the child when it was 1 month old was 2,000,000. Subsequently, the red cells of the child increased in number until at 9 months of age they numbered 4,200,000. A splenectomy was performed on the mother one month after the birth of her baby, and her red cell count returned to normal a few weeks after operation.

Some anemic anoxias are a *pleonectic* type: the hemoglobin attaches itself more readily to other radicals, excluding the oxygen component; or, the combination between the oxygen and the hemoglobin may be so fixed that an adequate amount of oxygen is not liberated. This deprivation of the cerebral tissue of its necessary oxygen can produce a serious anoxia.[2] Sulfanilamide in therapeutic dosage may displace as much as one-third of the hemoglobin in the blood, producing the characteristic cyanotic color changes.[13] The author has observed grave cerebral damage when a patient, whose temperature was elevated from infection, was given large doses of sulfanilamide, producing the attendant cyanosis, and was then exposed to nitrous oxide-oxygen anesthesia. In another case a mother with severe pneumonia was given large therapeutic doses of sulfanilamide the day preceding delivery. No anesthetic or analgesic drugs of any kind were used and, with the mother in an oxygen tent, the baby was born without difficulty. The baby remained markedly cyanotic for twenty-four hours, although the child was alert, cried, nursed well, and nothing unusual was noted neurologically. The color was good on the second day. Whether the cyanosis was due entirely to the sulfanilamide is conjectural, but there can be little doubt that the condition of the baby would have been more precarious had any anoxic factors been superimposed, such as dystocia or respiratory depression from analgesic drugs and anesthetics.

None of the instances of cerebral dysfunction in this group of defective children were considered *solely* due to the action of pleonectic agents. However, the possibility of such occurrences must be kept in mind if therapeutic adjuncts are used which form methemoglobin and thus deprive the blood of some of its oxygen-carrying capacity. A deficiency in carbon dioxide in the blood causes the hemoglobin to combine more tightly with oxygen, so that it is not available to the cerebral cells. This is of clinical significance in the resuscitation of the newborn infant and has been an effective argument for the employment of the carbon dioxide-oxygen mixture as advocated by Yandell Henderson.[2]

A less than normal *quantity* of blood circulating causes *stagnant anoxia*.[9] Failure of the heart to maintain the circulation adequately, either as the result of depression of the vital medullary centers or owing to the loss or absence of muscle tone, may produce this type of anoxia. A low blood pressure in the mother, the result of some constitutional deficiency or induced by depressing agents such as spinal anesthesia or heavy preoperative medication, may spell disaster for the baby still vitally dependent upon the maternal supply of oxygen.

Excessive pressure applied to the fetal head by marked dystocia or forceps will cause a stagnation of the cerebral circulation. Anoxic damage may result if the oxygen deprivation is acute or of sufficient duration. In our series, forceps and version extractions were employed

in many of the cases. Increased intracranial pressure, coexistent with cerebral edema or hemorrhage, whether intra- or extracerebral,[14] can produce a stagnant anoxia with consequent degenerative tissue change. Some of the babies with good color at birth became cyanotic (some repeatedly) during the first days of neonatal life. In these cases the anoxia seems to have been due to a delayed increase in intracranial pressure as a result of the factors mentioned, or to "fatigue" of the respiratory center. Trephine with subdural aspiration is indicated for the child in whom a localized blood or fluid collection in the subdural or epidural space produces delayed symptoms of anoxia.

Histotoxic anoxia occurs with the oxygen supply perfectly normal in all respects. Anoxia may nevertheless occur if the tissue cells are affected in such a manner that they cannot *use* the oxygen properly.[15] The biochemical reactions of the cells may be altered to this extent by drugs, anesthetics, or poisonous substances acting directly on neuronal tissue. In reviewing the birth histories of these children with evidence of cerebral damage, it was observed that a variety of analgesic drugs and anesthetic agents were employed in most of the cases. Since these are *optional* obstetric adjuncts, it is especially necessary to evaluate carefully their prominence in the production of asphyxia in the infant. Normally, without the employment of anesthetics or analgesic agents, approximately two out of every one hundred newborn babies do not breathe immediately; the use of drugs and anesthetics definitely increases the number exhibiting evidence of asphyxia at birth.[16] Cole and Kimball, in a report of a series of 5,000 cases, found that even acknowledged pharmacologic doses of scopolamine, morphine, or any of the barbiturates (quantities less than are generally employed for full analgesic dosage) influence the degree of asphyxia in the newborn babies, as well as the number of babies born with evidence of asphyxia.[17]

The question of the relation between interference of convenience, or necessity, and asphyxia must be considered. The neurologic surgeon who sees serious intracranial complications in babies, arising from seemingly slight head trauma, naturally views with suspicion the rapid molding of a soft skull and brain to fit the fixed grasp of a steel instrument whose only mechanical advantage is to squeeze and pull. This procedure, as well as version and extraction, would seem to duplicate some of the undesirable features of precipitate delivery.

However, there can be little doubt that with deep birth analgesia this type of interference saves the baby from some of the effects of prolonged intrauterine asphyxia. Just as the fireman enters a smoke-filled room, drags out a victim, and brings him back to life with artificial respiration, so the physician pulls the baby out of the drug-bound uterus by the head or the heels, and saves his life with oxygen. The only difference in the two situations is that the fireman did not set fire to the house!

An important group of cases classed as histotoxic anoxia results from an imbalance in the levels of the blood calcium and potassium, blood sugar, or in the blood chlorides of the mother or the baby. The latter may be referred for observation some time after birth when evidence of cerebral deficiency is exhibited. Recent researches into the matter of the organization of nervous tissue strongly emphasize the great importance of the maintenance of the proper chemical balance in all nervous tissue. Oxygen utilization is largely, if not solely, dependent on the neuronal integrity of the cellular chemical environment. If the proper biochemical balance is lacking, anoxic degeneration will result.[18] Bronk has stated, "Fundamental biological considerations demand that we consider cellular activity to be determined by the interplay of all the physical and chemical agents to which the cell is exposed."[10] We cannot ignore the importance of this declaration and its implications.

If the neurohumoral balance is upset by dehydration, cerebral oxidation may be interfered with to the extent of disastrous deprivation. The cerebral deficiency in a child whose mother suffered from pernicious vomiting during pregnancy can properly be suspected to be the result of anoxia caused by disturbance of the internal environment of cortical cell structure from dehydration; a history of eclampsia in the mother is not infrequent. It is probable that large doses of narcotic drugs given to the mother in the effort to control her convulsions have, in many instances, increased the anoxia concomitant with eclampsia in mothers.

A ten-year-old boy was referred by suburban school authorities because, without provocation, he had been knocking down smaller schoolmates. Punishment had not succeeded in controlling this practice, which began when he entered school at the age of 7. School psychologists reported an I. Q. of 75, but he was carried along with the regular classes because no special instruction was available. He appeared to be normal physically and, aside from a sly look when he answered questions, he did not seem mentally defective on casual examination. One week prior to his birth his mother suffered from frequently recurring convulsions, during which she became extremely cyanotic. Large and repeated doses of morphine failed to control the convulsions. Mitral heart disease and hypertension of long standing added to the seriousness of the mother's condition. Obstetric consultation deemed it expedient to deliver her baby (fetal age 8 months) by cesarean section. The mother and child survived the operation which was performed with deep ether anesthesia.

A similar etiology could be suspected in the first born of a pair of twins, a male child 9 months of age, with mental retardation and convulsions, who was seen shortly before death. The examination disclosed a generalized spasticity and lack of interest in surroundings.

The child had generalized twitchings and convulsions from birth until its death. Autopsy showed marked bilateral frontal lobe atrophy, with moderate hydrocephalus. The birth history, not an unusual one, showed that the mother, 24 years of age, a primipara, was admitted to the hospital in coma, with convulsions and cyanosis. Temperature was 99.4°; pulse, 140; and respirations, 36 per minute. The total amount of drugs given for the control of convulsions in the four and one-half days preceding delivery was: 1¼ gr. morphine (five ¼ gr. doses); 48 gr. sodium amytal (sixteen 3 gr. doses); 7½ gr. sodium amytal (one intravenous dose); 40 gr. chloral hydrate (two 20 gr. doses). The final drug administration was made at 12:30 A.M., and ether anesthesia was given at 3:34 A.M. for low forceps delivery of the first twin, who breathed spontaneously and cried well. Thirty minutes later low forceps were used to deliver the second twin, a female child, which was stillborn.

Careful examination of the paranatal records of mentally defective infants and children (for whom there was no history of inherited defect, infection, or trauma unassociated with birth) has disclosed a definite relationship between fetal oxygen want and the later neurologic defect. Since cerebral deficiency may occur as a result of cerebral anoxia, the controllable factors inducing asphyxia must be re-evaluated. Foremost among these are the optional drug and anesthetic agents used to produce analgesia and amnesia in the mother. The asphyxia resulting from the excessive use of drugs to produce unconscious labor is no less serious in its effect on the baby than that from any other cause. Any method of delivery which produces a defective infant has no compensation for the mother, the child, or the physician.

Studies of the function of cellular structure of nervous tissue support the view that a more realistic and philosophic viewpoint must take into consideration any and all factors which have a tendency to disturb or alter the chemical environment of the delicate nervous tissue of the newborn brain. The habit of consigning defective children in the early years of their existence into groups, largely for disposition of their physical welfare, should have as a basis a more extensive inquiry into the etiological factors responsible for the subnormal organism. The thesis of cerebral anoxia from asphyxia in the newborn infant cannot be unequivocally rejected as a causative factor in brain deterioration merely on the timeworn basis of developmental central nervous system defects. Many of these anomalous degenerative and atrophic changes have a biochemical explanation which determines their organic departure from the normal. "Birth asphyxia" is a term loosely applied in private and hospital practice. Adequate paranatal histories will become available when the present nomenclature is refined to provide exact terms with which comprehensive descriptions of the physical condition of mother and child can be made.

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HEART MURMURS IN NEWBORN INFANTS

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THE incidence and significance of heart murmurs in newborn infants have received little attention in the medical literature in the past. In the routine examination of a large number of newborn infants we have observed a group of 147 infants with heart murmurs and have been able to follow the course of more than half of these patients in later life. An analysis has been made of some of the possible predisposing causes of the condition.

MATERIAL AND PROCEDURE

During a four-year period, from November, 1934, through October, 1938, a total number of 7,673 newly born infants were examined on the Obstetrical Wards of the Cincinnati General Hospital. Not included in this group were stillborn infants, those dying within a few hours after birth, and premature infants weighing less than 5 pounds at birth. Complete physical examinations of the infants were made during the first twenty-four hours of their lives, and more frequently when indicated. During the past two years a second routine examination was made on the fifth or sixth day of life. When discharged from the hospital, the mothers were instructed to bring their infants back to the nearest of seven children's clinics maintained in various parts of the city. Not all of these examinations were made by us, but trained pediatrists were in attendance in every case. In some instances, calls were made at the homes of these patients to examine their hearts. Infants with persistent murmurs were referred to our children's cardiac clinics where roentgenograms, fluoroscopic examinations, and electrocardiograms were made.

RESULTS

Incidence.—Among a total number of 7,673 newly born full-term infants observed during the first week of life, 147 had cardiac murmurs, an incidence of 1.9 per cent. There were twenty-five additional infants who had some abnormality of cardiac rate or rhythm and were not considered in this report.

Race and Sex Distribution.—Heart murmurs were somewhat more frequent in the negro than in the white infants. The seventy-six white infants constituted 1.6 per cent of a total number of white full-term babies born during the period of observation, while the seventy-one colored infants with murmurs constituted 2.4 per cent of the total number of negro infants, a difference of statistical significance (Table I).

From the Department of Pediatrics, University of Cincinnati, and the Children's Hospital Research Foundation.

Murmurs occurred in seventy boys (1.8 per cent) and in seventy-seven girls (2.0 per cent), which seemed to be a fairly equal distribution

Month of Birth.—The infants with murmurs were classified according to the month of their birth, in the search for seasonal factors which might contribute to the incidence of the heart condition. The percentages of incidence varied from 1.0 to 2.7 in different months. Although there was a slight increase in the incidence of murmurs in the fall and winter months, the differences were not great, and further analysis of other factors would be necessary to prove that the different seasons with

TABLE I

THE INFLUENCE OF RACE, SEX, MONTH OF BIRTH, BIRTH WEIGHT, AND SYPHILIS UPON THE INCIDENCE OF HEART MURMURS OF NEWBORN INFANTS

	TOTAL NUMBER	NUMBER WITH MURMURS	PERCENTAGE
Entire Group	7,673	147	1.9
Race			
White	4,710	76	1.6
Black	2,963	71	2.4
Sex			
Male	3,895	70	1.8
Female	3,778	77	2.0
Month of Birth			
January	662	18	2.7
February	569	15	2.6
March	623	17	2.7
April	588	6	1.0
May	593	9	1.5
June	609	12	2.0
July	680	7	1.0
August	754	13	1.7
September	646	12	1.9
October	681	13	1.9
November	664	16	2.4
December	604	9	1.5
*Birth Weight**			
5 lb. to 5 lb. 15 oz.	635	14	2.2
6 lb. to 6 lb. 15 oz.	1,570	29	1.8
7 lb. to 7 lb. 15 oz.	1,956	46	2.4
8 lb. to 8 lb. 15 oz.	1,024	18	1.8
9 lb. to 9 lb. 15 oz.	296	12	4.1
10 lb. and over	84	2	2.4
*Syphilis**			
Total number of white mothers tested	2,861	54	1.9
Number with positive serologic reactions	152	2	1.3
Total number of black mothers tested	1,617	50	3.1
Number with positive serologic reactions	228	6	2.6

Note: The only group in which differences of incidence of murmurs seemed great enough to warrant statistical analysis was that of race. Employing the X^2 formula, values of p were found to be .01 to .02. Therefore, the racial distribution noted above could only rarely have arisen from chance alone, and the difference of incidence of murmurs in the two races was statistically significant.

*Figures of birth weights and syphilis include a three-year period instead of the four-year period recorded under race, sex, and month of birth.

the accompanying variations of diet and vitamin intake influenced the occurrence of murmurs in newborn infants.

Birth Weight.—The possibility that heart murmurs would occur with greater frequency among less mature or underweight infants was not borne out in this survey. Murmurs were a little more frequent in infants weighing from 9 to 10 pounds than in the other weight groups, but there was no definite trend of increased frequency in either the heavier or lighter infants (Table I).

Illness of the Mother During the Prenatal Period.—Syphilis of the mother was determined by Wassermann or Kahn tests of her blood serum during the prenatal period. The incidence of murmurs in the infants of the entire group of white mothers was 1.9 per cent, and in those of the mothers who had positive serologic tests, only 1.3 per cent. In the infants of negro mothers, the incidence of murmurs was 3.1 per cent in the entire group and 2.6 per cent in those with positive serologic reactions (Table I). Syphilis apparently played no role in the cause of cardiac murmurs of newborn infants.

It would be of interest to know whether *other illnesses of the mother,* such as the toxemias of pregnancy, had any influence upon the occurrence of heart murmurs in their offspring. Data of this type were incomplete for this survey, but a study of this question has been undertaken and will be reported later.

Characteristics of the Murmurs.—Almost all of the murmurs heard in this series of newborn infants were systolic in time. In only two instances was there a diastolic murmur heard in conjunction with a systolic one. The murmurs were blowing in quality in about half of the group, and in the other half they were rough or musical. The majority were audible over the entire precordium and were usually heard loudest at the apical area or in the region of the third costal interspace a little to the left of the sternum.

Many of the murmurs were transitory during the first week of life. Eighty-four infants of the total number of 147 were followed carefully in regard to the permanency of the murmur during the first week. In forty-one cases (49 per cent) a murmur was heard during the first twenty-four hours of life, but had disappeared by the third to sixth day. In twenty other instances (24 per cent), the murmurs were heard on both the first and sixth days of life, and in the twenty-three remaining infants (27 per cent), the murmur was not noted on the first day, but was heard on the fifth or sixth day only.

Subsequent Course.—The course of 92 infants of the total group of 147 could be followed after dismissal from the hospital (Table II). Death occurred in four instances. One infant who died on the fourth day of life had a cor biloculare; one who died at the age of 2 months had auricular and ventricular septal defects, a patent ductus arteriosus, and dilatation of the pulmonary artery. The third infant died at the age

of 9 months of gastroenteritis, and no autopsy was obtained; the last child died at home of undetermined cause.

TABLE II

SUBSEQUENT COURSE OF NINETY-TWO INFANTS WITH HEART MURMURS

COURSE	NUMBER OF INFANTS
Died (4)	
Congenital heart disease proven at autopsy	2
Gastroenteritis. No autopsy.	1
Cause of death not known	1
Followed in Later Life (88)	
Persistent murmurs	14 (16%)
Inconstant, functional murmurs	2
Extrasystoles	1
Entirely normal	71

The remaining eighty-eight infants were observed in their homes or at clinics after their dismissal from the hospital. Thirty-one were seen only once; thirty-six were examined from two to ten times; and twenty-one were observed on more than ten occasions. Practically all of these infants were examined about six months after dismissal from the hospital, and more than half of the group, forty-five infants, were followed until they were over 1 year of age.

The murmurs had persisted in fourteen instances, or 16 per cent, of the eighty-eight infants followed. In three patients a patency of the interventricular septum was suspected, but in the other patients no definite diagnosis could be made. Mild cyanosis was noted in two infants.

In the remaining seventy-four patients of the group of eighty-eight infants who survived, the hearts seemed normal except for inconstant systolic murmurs in two instances and extrasystoles in one other. No distinctive signs occurred during the first week of life to indicate which murmurs would persist for the longer periods of time. The quality of the murmurs and their location during the first week were practically the same in the groups of infants with permanent murmurs as in those with temporary murmurs. Roentgenograms did not give much assistance in the diagnosis of congenital heart disease during the neonatal period of this series of infants, but their routine use is advocated to detect associated pulmonary lesions and to observe the heart size and configuration. With electrocardiograms some irregularities of cardiac rhythm were detected, but very little help was obtained from them in ascertaining the type of congenital deformity.

DISCUSSION

Although the occurrence of heart murmurs in newborn infants has been mentioned occasionally in the medical literature, no statistical reports of the incidence of the condition could be found. Differences of opinion exist in respect to the significance of these murmurs. Von Reuss[1] stated that any definite murmur heard in a young infant who

was quiet during the examination indicated the presence of a congenital cardiac defect, and that functional murmurs at this age were extremely rare. A similar opinion was expressed in the White House Conference Reports.[2] Wüsthoff[3] also thought that most of the murmurs occurring during the neonatal period represented congenital heart lesions, but that in cases of doubt the organic murmurs could be differentiated from functional ones by the harsh, loud quality of the former which was heard over the entire precordium and back, independent of respiration or position. On the other hand, Owen and Kingsbury[4] considered functional murmurs to be fairly common in newborn infants. They had noticed temporary blowing murmurs at the base of the heart or in the mid-cardiac area in newborn infants, and frequently in premature infants with jaundice. The murmurs of the latter group usually disappeared as the jaundice faded. Grulee and Bonar[5] believed that some of the murmurs heard in newborn infants were functional in type, especially those which were transient and were apt to occur only when the heart rate was accelerating. Dunham[6] has stated that murmurs occurred frequently in newborn infants and often tended to disappear and recur at later periods. She believed that many of these murmurs were functional in character.

The incidence of congenital heart disease found at autopsy by different investigators has varied from 2.3 to 11.6 per cent of infants and children and from 0.85 to 8.1 per cent of groups including patients of all ages (Table III). The incidence of heart murmurs which we

TABLE III

AUTOPSY EVIDENCE OF CONGENITAL HEART DISEASE IN VARIOUS AGE GROUPS OF CHILDREN AND ADULTS

AUTHOR	AGE GROUP	TOTAL NUMBER OF AUTOPSIES	NUMBER OF PATIENTS WITH CONGENITAL HEART LESIONS	PERCENTAGE
Philpott[7]	1-28 days	759	36	4.7
McGinn[8]	1-28 days	70	7	10.0
Gibson and Clifton[9]	Under 1 mo.	189	22	11.6
Terplan and Sanes[10]	0-1 yr.	336	21	6.3
Gibson and Clifton[9]	1 mo.-1 yr.	829	52	6.3
Philpott[7]	1 mo.-2 yr.	957	27	2.8
Dolgopol[11]	1 mo.-2 yr.	210	14	6.6
McGinn[8]	1 mo.-2 yr.	140	7	4.7
Gibson and Clifton[9]	1-2 yr.	276	12	4.3
Gibson and Clifton[9]	2-5 yr.	331	10	3.0
Gibson and Clifton[9]	6-9 yr.	216	5	2.3
Gibson and Clifton[9]	10-12 yr.	109	4	3.7
Epstein[12]	0-13 yr.	1,000	40	4.0
Dolgopol[11]	All ages (over 2 yr.)	872	50	5.7
Philpott[7]	All ages (over 2 yr.)	5,522	17	0.3
Abbott[13]	All ages	3,633	43	1.2
Leech[14]	All ages	13,115	170	1.29
McGinn and White[15]	All ages	7,500	67	0.9
Rannels and Propst[16]	All ages	4,255	36	0.85
Jacobius and Moore[17]	All ages	1,600	131	8.1

noted during the neonatal period (1.9 per cent) is less than half of that of congenital anomalies of the heart found at autopsy in the first month of life (4.7 to 11.6 per cent). Probably a number of infants with congenital heart lesions have no symptoms at birth.

The incidence of congenital heart disease has been reported in cardiac clinics, which do not represent a true cross section of the total population. Reports of school surveys, which furnish the most reliable samples of population, include only age groups between 5 and 18 years. Here the incidence of congenital heart disease has ranged from 0.5 to 0.15 per cent (Table IV) which is considerably lower than the incidence of murmurs suggestive of congenital heart disease which we found in newborn infants (1.9 per cent), and of the permanent murmurs noted in later months of infancy (16 per cent of the eighty-eight followed or an incidence of 0.3 per cent of the entire group of 7,673 infants). It would seem that either a greater number of the murmurs of infants are functional in type than our findings indicate or that many infants with congenital lesions do not survive to school age.

TABLE IV

CLINICAL EVIDENCE OF CONGENITAL HEART DISEASE IN VARIOUS AGE GROUPS OF CHILDREN

AUTHOR	AGE GROUP	TOTAL NUMBER OF CHILDREN	NUMBER WITH EVIDENCE OF CONGENITAL HEART DISEASE	PERCENTAGE
Boston School Survey[18]	6-18 yr.	119,337	69	0.05
Cahan[19]	6-18 yr.	10,333	9	0.09
Sampson, Christie, and Geiger[20]	6-18 yr.	13,338	19	0.14
Rauh[21]	6-18 yr.	85,389	131	0.15

It is interesting to speculate on the possible causes of the heart murmurs in newborn infants. If the murmurs at this period of life are due to the persistence of fetal structures, such as the ductus arteriosus or the foramen ovale, or to readjustments of pulmonary circulation, the incidence of the abnormal heart sounds should be greater. Complete readjustment of circulation is not established generally until the infant is two months of age or older. In the autopsies reviewed by Leech,[14] the ductus arteriosus either was closed by the fourth month of life or remained permanently open. Christie[22] found the ductus closed in 88 per cent of patients by the eighth week of life and the foramen ovale closed in 87 per cent of infants by the twelfth week of life. According to Patten,[23] functional closure of the foramen ovale occurred in practically all cases by the third month of life, although true closure occurred more slowly and the passage of a probe through the opening was possible in 25 per cent of adults. The pressure of the left side of the heart becomes equal to that of the right side by the third to fifth month of life, but it does not become greater until the child is about 7 years of age.

Since the majority of infants have a patency of the foramen ovale and ductus arteriosus in the early weeks of life and the incidence of murmurs in our series was only 1.9 per cent, we conclude that these remnants of fetal circulation rarely produce cardiac murmurs.

Many cardiac anomalies cannot be detected or diagnosed with accuracy in the first few weeks of life. Abbott[24] has state that the type of congenital lesion can rarely be determined before the second year of life. McGinn and White[15] found that twenty-five of a group of forty-one patients with congenital heart disease proved at autopsy had had no clinical signs which would permit an accurate diagnosis before the death of the patients. Gibson[9] has reported that many children of the younger age groups in whom a patent ductus arteriosus was discovered at autopsy had had no murmurs or atypical ones during life. In eleven of the twelve children of his series with interventricular septal defects, however, typical murmurs of harsh systolic types had been heard in the precordial area, loudest in the third left interspace near the sternum.

SUMMARY

Heart murmurs were detected in 147 infants (1.9 per cent) of a series of 7,673 newborn infants examined during the first week of life.

The sex of the infant, the month of birth, the birth weight, and the occurrence of syphilis in the mother did not seem to influence the incidence of murmurs.

The murmurs were more frequent in the negro than in the white infants.

Of the group of 147 infants with murmurs, 92 were followed later in life. Four had died, and heart disease was found in the autopsies of two of these infants. Fourteen had persistent systolic murmurs which were considered to represent some form of congenital cardiac lesion. Of the seventy-four remaining patients, seventy-one were entirely well without any clinical evidence of heart disease and three had functional murmurs or extrasystoles.

The incidence of congenital heart disease in previous reports of autopsy records and school surveys has been reviewed and comparisons with our observations indicate that:

1. In the period of readjustment of circulation during the first few weeks of life, patencies of the foramen ovale and of the ductus arteriosus usually do not produce clinical cardiac murmurs.

2. Many other congenital anomalies of the heart do not cause murmurs during the neonatal period.

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VENTRICULAR DILATATION IN SPINA BIFIDA

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THE purpose of this paper is to show evidence of ventricular dilatation in neonates and infants with spina bifida and meningocele or myelocele, prior to operative interference. There are six cases, but the consistency of the ventricular findings is striking. All infants showed true spinal defects.

The ventriculograms were planned to be done as soon as the infant returned to birth weight, but for various reasons occurred anywhere from the fifth day to the sixth week of life. No attempt was made to fill the ventricular system. Approximately 30 c.c. of cerebrospinal fluid was removed, and 25 c.c. of air injected.

All the ventriculograms were done in the face of relatively normal head measurements. To look at most of these infants at the time, dilated ventricles would hardly have been suspected. Myers' figures for head circumference, as quoted by Bucy[1] in *Brenneman's System of Pediatrics*, were taken as normal. These give the occipitofrontal circumference from birth to the first month of life as 13.7 to 14.1 inches; and the measurement from the first to the second month as averaging 14.9 inches.

Routine care of the sac has been first to flush it gently with sterile water, then to dry and cover with a thick layer of collodion followed by vaseline gauze, and to keep the infant on its side or abdomen.

CASE 1.—Baby Le C. had a full-term normal delivery. At birth a small, sessile, bluish-red sac was noted over the lower lumbar region. At this time the head appeared normal, measuring 13⅝ inches. There was no lower extremity paralysis, and the sphincter tone appeared good. The head became larger, measuring 14⅛ inches on the fifth day. On this day occurred an unexplained fever. Because of this, the ventricles were tapped, and the thinness of the cortical tissue was noted. The cerebrospinal fluid removed was normal. Ventriculogram was done on the seventh day of life (Fig. 1).

The infant was discharged when two weeks old, the head measuring 14⅛ inches. The extremities appeared slightly spastic. The temperature was normal. (This child was discharged because of the dilated ventricles. In view of later experience, we would probably have suggested operation. The subsequent course of this infant is unknown.)

CASE 2.—Baby girl A. was a full-term infant weighing 7 pounds and 2 ounces. At birth a sac was noted about the eighth dorsal vertebra. There was definite lower extremity paralysis. Ventriculogram was done at 1 month of age; the head then measured 14½ inches (Figs. 2 and 3). The infant died at six weeks of age after ten days of intermittent fever due to meningitis.

From the Pediatric Service, Mary Immaculate Hospital.

CASE 3.—Baby boy L. was admitted to the hospital at 4 days of age. A sac, 3 by 3½ inches, was present over a bony defect in the first and second lumbar vertebrae. Motion in the legs was definitely impaired. There were bilateral clubfoot and urinary dribbling. At 14 days of age, the head measured 13¾ inches. Ventriculogram was not done until the infant was 6 weeks old, the head then measuring 14½ inches (Figs. 4 and 5). Three days after the ventriculogram, the head circumference had increased to 15¼ inches. Operation was attempted at this time, but the infant died three days later with bronchopneumonia and meningitis.

CASE 4.—Baby girl S. was a full-term infant weighing 7 pounds and 9 ounces. At birth a large sac was noted extending along the lumbar region. There were clubbing of the feet, paresis of the extremities, and apparent insufficiency of the bladder and rectal sphincters. At 17 days of age, a ventriculogram was done; the head then measured 13¼ inches (Fig. 6).

No surgery was attempted. At 2 months of age, the head measured 15⅛ inches. The infant died at 4 months of age with an obvious progressive hydrocephalus and with an intermittent and unexplained fever occurring during the last month of life.

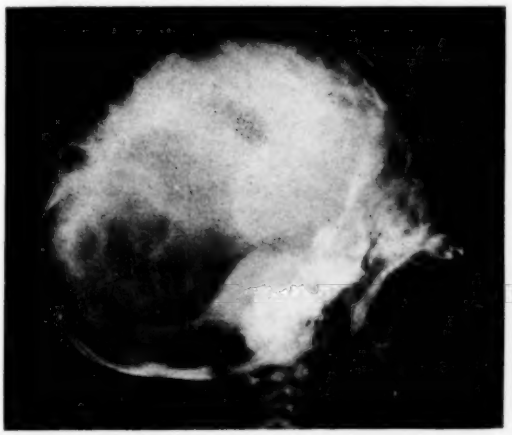

Fig. 1.—Case 1. Ventriculogram done on the seventh day of life. Note marked dilatation of the lateral ventricles. Head circumference, 14⅛ inches.

CASE 5.—Baby girl I. was a full-term infant weighing 6 pounds and 4 ounces. At birth a large fist-sized sac was noted extending from the sacrum to the first lumbar vertebra. There was clubbing of the feet, but no paresis of the extremities. Sensation over the extremities appeared intact. The head measured 13½ inches on the fifth day of life when the ventriculogram was done (Fig. 7).

On the tenth day, the sac was excised and the defect repaired. No nerve tissue was present in the sac. The postoperative course was uneventful. This child is now about 2 years old. Save for the clubbed feet, she is normal physically and mentally. There is no hydrocephalus.

CASE 6.—Baby boy P. was admitted to the hospital at 1 month of age. A lumbar sac had been present since birth, with inability to move the lower extremities.

Successive head measurements on the second, fourth, and tenth days after admission were 14½, 14⅜, and 14⅞ inches, respectively. Ventriculograms had been done on the second day after admission (Figs. 8 and 9).

Fig. 2.—Case 2. Ventriculogram at 1 month of age. Anteroposterior view. Note ventricular dilatation. Head circumference, 14½ inches.

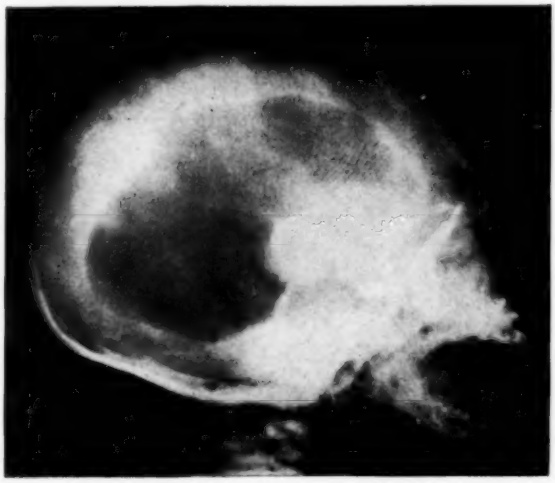

Fig. 3.—Case 2. Lateral view of ventricles.

Operation on the tenth day (at 5 weeks of age) revealed a myelomeningocele. The sac was left intact. The postoperative course was rather stormy, and within two weeks the head circumference had increased ¾ inch. The infant was discharged five weeks postoperatively. Good function was slowly returning to the legs.

Fig. 4.—Case 3. Ventriculogram at 6 weeks of age. Anteroposterior view. Dilated lateral ventricles. Head circumference, 14½ inches.

Fig. 5.—Case 3. Lateral view of ventricles.

This child is now about 1 year old. The head is slightly enlarged, but the child appears mentally normal. There is still good function in the lower extremities. (Fluids have been markedly restricted throughout the year, and a regime of dehydration supplemented by thyroid extract and diuretin has been followed.)

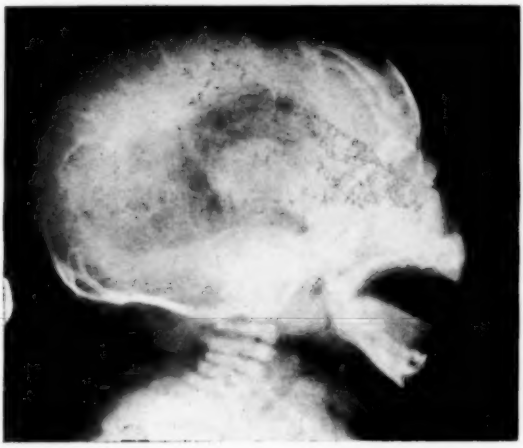

Fig. 6.—Case 4. Ventriculogram at 17 days of age, showing dilatation of lateral ventricles. Head circumference, 13¼ inches.

Fig. 7.—Case 5. Ventriculogram at 5 days of age. Marked ventricular dilatation. Head circumference, 13½ inches.

COMMENT

It has long been known that progressive hydrocephalus is a frequent concomitant of the severer grades of spina bifida, and clinically it has been noted that operation will precipitate the onset. Much discussion has centered about the preservation of the sac in an effort to retain its

Fig. 8.—Case 6. Ventriculogram at 5 weeks of age, with similar dilatation of ventricles. Head circumference, 14½ inches.

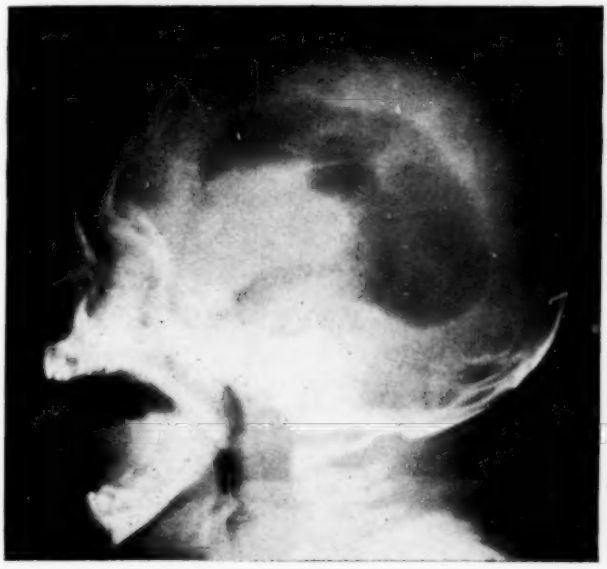

Fig. 9.—Case 6. Lateral view of ventricles.

absorptive function and to avoid disturbing the hydrodynamics of an unstable system. (Penfield and Cone.[2])

In the above cases the marked dilatation of the ventricles was surprising, especially in view of the head measurements and the clinical appearance of these infants. Moreover, two of the infants have done relatively well, despite at least an equal degree of ventricular dilatation as those who went on to progressive hydrocephalus. This supports Gross' and Sachs'[3] contention that "hydrocephalus does not occur after operation as frequently as has been supposed, though one can never tell beforehand in which case it may appear."

The obvious question is whether or not all children with even a mild degree of spina bifida and simple meningocele have a similar ventricular dilatation. There is no direct evidence on this point since the milder cases have generally done well. But that some degree of ventricular dilatation may exist and not be apparent clinically is brought out by the necropsies of Gross and Sachs.[3] In their nonoperative group of thirty-six fatal cases, which were undoubtedly the most severe types, hydrocephalus was demonstrable in seventeen of nineteen autopsies. In the remaining seventeen cases in which necropsy was not permitted, hydrocephalus was present clinically in but seven. Since the causes of death were approximately the same for both groups, we may assume that at least 90 per cent of the second group would also have shown some ventricular dilatation at postmortem. Similarly, Keiller,[4] in her dissections on five cases of spina bifida, reports three in which no hydrocephalus was found. In two of these, hydrocephalus was clinically absent, but there was no postmortem examination of the head. The protocol of her third case reports dilated ventricles, despite the absence of clinical hydrocephalus. From the above ventriculograms we would anticipate some degree of ventricular dilatation in all cases of spina bifida, except spina bifida occulta.

Throughout the discussion we have avoided qualifying the dilatation of the ventricles as hydrocephalus, i.e., of an obstructive nature, although it is very probable that this is the most common mechanism. The exact cause of the obstructive phenomena is not altogether clear. Bucy,[1] citing Woltman and others, believed that a failure in cleavage of the periencephalic mesenchyme gives rise to a communicating type of hydrocephalus, and that the spina bifida is a coincident anomaly, also dependent upon failure of normal cleavage.

Recently, Russell and Donald[5] have carefully investigated ten cases of spina bifida and hydrocephalus. In two cases there was a definite atresia along the ventricular pathways, one aqueductal and the other in the fourth ventricle. In the remaining eight cases they emphasized an anomalous displacement of the fourth ventricle and tip of the cerebellum downward over the upper segments of the spinal cord. They

noted the elongated medulla and the upward radiations of the lower cranial and upper cervical nerve roots. The spinal fluid appeared to be shunted into the spinal subarachnoid space instead of filtering out into the basilar cisterns, and was prevented from reaching the latter by the structures filling the foramen magnum. This anomalous situation had been independently described many years ago by Arnold and Chiari, and has since been known as the Arnold-Chiari malformation. Recently, Penfield and Coburn[6] have described its existence in an adult, whose upper thoracic spina bifida had been operated upon at an early age. They felt, however, that the degree of ventricular dilatation found at post-mortem was due to traction on the cord giving rise to a functional lower aqueductal obstruction.

Such a mechanism could not be determined by these ventriculograms, since air, especially in the small quantities used, would rarely reach the subarachnoid cisterns. Encephalography with its ability to demonstrate an air-containing encephalic space would be of help. But this would be a trying procedure in an infant, and not without danger, should it be attempted through the cistern and should the above mechanism exist.

We realize that hydrocephalus is often apparent only as growth progresses, and that there are valid objections to assuming that normal measurements during the first few weeks of life are of much significance. Unfortunately, the clinical data were not questioned sufficiently concerning the contents of the sacs, although four cases, because of the paralysis, seem definite myelomeningoceles. Nor were we aware of the Arnold-Chiari malformation at the time post-mortems were done.

We believe the air injections have some anatomic value. Anticipating these findings even in most cases of simple meningocele, ventriculography should be a routine where many of these conditions are encountered. To our mind it casts some doubt on the theoretical advantages of preserving the sac, save for its nerve content. Finally, in all cases without too marked a neurologic or physical defect, repair should be attempted as soon as possible.

CONCLUSIONS

Ventriculograms done within the first few weeks of life, on a group of infants with spina bifida are presented.

It is suggested that ventricular dilatation is more common than has been supposed.

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90-26 150TH STREET

PROPHYLAXIS AND TREATMENT OF POLIOMYELITIS WITH NEOPRONTOSIL

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IN NOVEMBER and December, 1938, eight cases of poliomyelitis were admitted to Roper Hospital. These were followed by several cases per month in January, February, and March, and by the anticipation of an epidemic with the advent of warm weather. With that in prospect, nothing hopeful was offered to date in the way of prevention or treatment of the acute process, although Jungeblut's experiments[1] suggested that an optimum vitamin C intake might be of value. It was, therefore, decided to try sulfanilamide and its derivatives, in spite of the negative results obtained in experimental animals.

Observation of some of these earlier cases treated on the hospital service showed that it would be very difficult to arrive at any definite conclusion as to the value of treatment given at various stages after the onset of paralysis. Every case differs in degree of involvement even without treatment of any sort, and it is very easy to be misled by a few cases.

Therefore, thought was given to the question as to what would constitute proof of inhibition of the virus of poliomyelitis, after its human host had begun to show symptoms of invasion. To answer this there is not much to go on except its action in inhibiting the growth and activity of the *Streptococcus hemolyticus* and other infections in which it is known to be effective. One might, I think, conclude fairly, if the drug inhibited the growth and activity of the virus of poliomyelitis, that (1) the temperature and toxemia would begin to subside within a period of 48 hours; (2) no increase of paralysis should take place after an adequate administration of the drug for 36 to 48 hours, if proper maintenance dose was kept up; (3) if the drug could be given in adequate dosage for a period of 24 to 48 hours before paralysis occurred and could be maintained over the "dangerous period," no paralysis should occur; (4) if the drug was given in the period before meningeal or paralytic involvement, and 48 hours of adequate dosage obtained before such involvement, and adequate maintenance dosage obtained over the dangerous period, no involvement should occur.

By these criteria, I was led to try the use of neoprontosil in private practice in an attempt to determine whether it was of value, with particular emphasis on its prophylactic value (4, above), and the prevention of paralysis in the group with meningeal manifestations sufficient to make a positive diagnosis, during an epidemic (3, above). Neoprontosil was originally selected because of the development of

mild idiosyncrasy, especially skin rashes, in a few of the earlier cases treated with sulfanilamide. This was comparatively rare in the entire series on neoprontosil.

Early in the epidemic, which developed in the latter part of April, it was found that every sick child must be considered as a potential case of poliomyelitis if the drug was to be given an opportunity to demonstrate any prophylactic value. There is no way of making a clinical diagnosis of poliomyelitis before meningeal symptoms or paralysis occurs. This is in accord with the experience of others, and virus has been recovered from children, associated with cases of poliomyelitis, having indefinite illnesses.[2] Symptoms in many may be quite suggestive, but many other children are seen in which the early symptoms are quite misleading and apparently not at all suggestive of poliomyelitis. I had the misfortune of having three of these develop paralysis twenty-four hours later, when I had not thought the symptoms sufficient to warrant giving neoprontosil. Once the presence of an epidemic was known to the community, sick children were seen much sooner than in the earlier phase of the epidemic.

The program adopted was to give neoprontosil, approximately 1 grain to the pound of body weight per day, divided into convenient dose schedule, every 3 to 4 hours. This dosage was usually given day and night until fever and toxemia had subsided for a period of twenty-four hours. Then the midnight dose was omitted, but the other doses were kept up over a period of seven days from the onset of the illness. Experience showed that this seemed to maintain adequate concentration, and was more likely to be followed in the home than if the midnight dose had been required for the full week. When positive central nervous system symptoms were present or when the disease was strongly suspected, the full dosage was continued for a longer period (until subsidence of symptoms), and then it was tapered off as in streptococcus infections.

From April 1 to August 31, 1939, the drug was given in the above manner to 440 sick children in Charleston, city and county, which has a total population of approximately 101,000.* The largest majority of these children had sore throat, headache (frontal), nausea, vomiting, and fever as the chief symptoms. Others had a preponderance of gastrointestinal symptoms—nausea, vomiting, diarrhea, and abdominal pains, associated with some sore throat and fever. This epidemic has been characterized by definite throat involvement in most of the cases diagnosed as poliomyelitis. During this time only one of these 440 children developed paralysis (Case 3 below), and this occurred after the mother had dropped dosage below maintenance level, when initial symptoms

*To date there have occurred in this area, during the current epidemic, 174 cases of poliomyelitis, of which 32 were nonparalytic and 142 were paralytic. There have been 11 deaths from poliomyelitis during this time.

subsided. In two other children (Cases 7 and 8) on neoprontosil therapy in whom the dosage was likewise dropped below maintenance level, meningeal symptoms developed on the fifth day but subsided without paralysis on return to full dosage. Three others (Cases 4, 9, and 13) developed meningeal symptoms within less than forty-eight hours after the drug was begun, but subsided promptly without paralysis. During this time, I saw and treated eleven (11) children with poliomyelitis who had paralysis present at the time when first given neoprontosil. These include three who developed paralysis within twenty-four hours after my first visit, who were not put on neoprontosil at that visit because symptoms were not at that time considered suggestive of poliomyelitis. They contributed largely to the realization that a diagnosis, in the absence of central nervous system symptoms, was impossible in most cases and that during an epidemic all sick children should be regarded with suspicion. These eleven cases varied in severity from early cases with slight involvement when first seen to two severe fulminating cases seen late, on admission to the hospital from adjoining counties. These two had rapidly advancing lesions with all extremities practically completely involved, and more or less complete involvement of respiratory tracts. In all of these the temperature and toxemia were subsiding or subsided within thirty-six to forty-eight hours. There was no apparent increase in paralysis after thirty-six to forty-eight hours of adequate drug treatment with neoprontosil. With the assistance of the Emerson respirator, the two patients, with rapidly advancing type of the disease, survived the acute disease. One of these died suddenly, approximately two months later, when beginning to recover some respiratory function (apparently from an attack of asthma, from which she had suffered for several years). The other child is still in the respirator.

The following cases of poliomyelitis treated with neoprontosil before paralysis had occurred are reported serially, as seen during the epidemic:

CASE 1.—D. M., female, aged 5 years, was seen at Roper Hospital in consultation, April 29, 1939. Illness began four days before with low-grade fever and some cervical adenitis. She had been given small doses of neoprontosil and seemed to be improving. Symptoms began with severe headache and stiffness of neck about 4:30 A.M. Headache continued, the fever rose, and she was brought to the hospital in the afternoon. Examination revealed congested throat, moderately enlarged cervical glands, and stiffness of neck. Knee jerks were active. Kernig sign was positive bilaterally. There was no paralysis. Otherwise the examination was negative.

Spinal Fluid.—On April 29, 1939, examination revealed 2,004 cells, polymorphonuclears 94 per cent, and lymphocytes, 6 per cent; globulin, 3 plus; sugar, 1 plus. No organisms were found by direct smear; Wassermann test was negative. A day later the spinal fluid showed 207 cells, 53 per cent polymorphonuclears and 47 per cent lymphocytes; globulin was 1 plus, sugar, 2 plus; culture, negative.

Treatment.—Because of high cell count and polymorphonuclear leucocyte count in the spinal fluid, antimeningococcus serum was given, 20 c.c. intramuscularly and 20 c.c. intravenously. She suffered a severe anaphylactic shock with near disaster after the latter. Following this, she was given neoprontosil solution (2.5 per cent) 7.5 c.c. intramuscularly every four hours until the next morning when it was given by mouth as tablets, 7½ grains every four hours until May 3, then 5 grains every four hours until May 6.

Progress.—Her temperature was 103° F. on admission the evening of April 29; it was normal on May 2; and toxic symptoms subsided. Stiffness of the neck and the back subsided gradually during the next few days. She was discharged to go home May 8, with no paralysis. She had serum sickness May 8, 1939.

CASE 2.—A. L., male, aged 8 years, was admitted to the hospital April 30, 1939. The illness began April 28 with headache and fever, and continued, the headache becoming progressively worse. He vomited the morning of admission. There was no pain in the abdomen, no diarrhea, or constipation. Physical examination showed well-marked photophobia; injected pharynx; slightly stiff neck; active knee jerks, 2 plus; slight Kernig, 1 plus; rapid heartbeat; no muscular weakness. On April 30 the spinal fluid contained 554 cells, 12 polymorphs, 88 lymphocytes; globulin, 1 plus; sugar, 2 plus. The Wassermann test was negative, colloidal gold test, negative; culture, negative.

Treatment.—Tablets of neoprontosil, 10 grains every four hours, were given from April 30 to May 7, 1939.

Progress.—The temperature was 104° F. on admission April 30 and was normal on May 2, 1939. The symptoms subsided entirely in a few days. There was no paralytic involvement.

CASE 3.—E. A. L., female, aged 3 years, was admitted to the hospital May 9, and discharged May 25, 1939. She was seen at home on May 4 with fever and a sore throat. Neoprontosil, 5 grains every four hours, was prescribed. The fever subsided the next day, but the mother did not give tablets regularly and the temperature rose again. Fever rose higher the night of admission, and when the child was awakened for medicine, she held her head on the left side and could not use her hands well. She was awkward and had a coarse tremor of the hands and the arms. Physical examination revealed weakness of neck muscles (right), neck drawn to left (it can be straightened up, but it drops back to left); neck not stiff; bilateral ataxia of arms; uncertainty of movements but no apparent paralysis. The knee jerks were present; Kernig sign, absent. The spinal fluid (May 9) contained 55 cells, 64 polymorphs; 36 lymphocytes. Tests for globulin and sugar were negative. Culture was negative also.

Treatment.—Neoprontosil, 5 grains every four hours, was prescribed and given from May 9 to 15, 1939.

Progress.—Her temperature which was 103° F. on admission on the evening of May 9, was normal on morning of May 11. There was no further paralytic involvement. The ataxia of the arms cleared in few days and by May 17, she was able to hold her head up well and apparently had completely recovered when discharged May 25, 1939.

CASE 4.—H. C., Jr., male, aged 17 years, became ill with fever, headache and sore throat on May 4, 1939. The headache was frontal and moderately severe; the temperature was over 102° F. His throat was congested, but physical examination was otherwise negative. He was given neoprontosil, 10 grains every four hours. Two days later, after a drop in the temperature, when he had felt somewhat better the day before, the temperature went up to 103° F., the headache became severe and slight rigidity of neck and back developed. He was considered

as probably receiving insufficient neoprontosil; the dose was increased to 20 grains every four hours for the next two days. The fever began to subside in 24 hours, headache decreased in intensity, and the neck became less stiff. Spinal puncture on May 8, showed that the fluid was clear, colorless, with 61 cells, lymphocytes predominating. Globulin test was negative, test for sugar, 1 plus. Neoprontosil, 15 grains every four hours, was continued until May 11, and then 10 grains every four hours was administered for three more days.

Progress.—Symptoms subsided rapidly with no paralytic involvement.

Of interest is the fact that his brother, 9 years old, had poliomyelitis beginning April 22, 1939, with paralytic involvement on the sixth day of illness, and his sister, 14 years old, began with headache, fever and sore throat May 3, 1939 (one day before patient) and vomited several times the first day. She was given neoprontosil, 10 grains every four hours. Fever and headache subsided in forty-eight hours, and there was no further disturbance. Neoprontosil was continued seven days.

CASE 5.—L. R., III, male, aged 8 years, was admitted to the hospital on May 10 and discharged May 24, 1939. The illness began with fever, nausea, and vomiting on May 8. He complained of soreness of neck the day before admission and headache and stiff neck on the day of admission. Physical examination showed well-marked stiffness of the neck; slightly positive Kernig sign; active knee jerks; congestion of throat and no muscular weakness. On May 10 spinal fluid contained 20 cells, 66 polymorphs, and 34 lymphocytes; globulin, 1 plus; sugar, 1 plus. Culture was negative.

Treatment.—Neoprontosil, 10 grains every four hours, was given from May 10 to 15, 1939, then 5 grains every four hours until May 19.

Progress.—His temperature on May 10 and 11 was 100 to 101° F. and was normal on May 13. The symptoms subsided within a few days and there was no paralytic involvement.

CASE 6.—M. D., female, aged 7 years, was admitted to the hospital on May 15 and discharged June 5, 1939. The illness began with fever on the evening before admission, and she complained of a sore throat the morning of admission. The fever continued, and her neck became stiff that afternoon. Physical examination showed congestion of the throat, stiff neck and back, positive Kernig sign, hyperactive knee jerks, and no muscular weakness. On May 15 the spinal fluid contained 125 cells, 60 polymorphs, 40 lymphocytes; globulin, 1 plus; sugar, 2 plus. The culture was negative.

Treatment.—Neoprontosil, 10 grains every four hours, was given from May 15 to 20, then 5 grains every four hours until May 22, 1939.

Progress.—Her temperature dropped from 100 to 101.5° F. on May 15 to normal on the morning of May 18. There was no paralytic involvement and symptoms subsided rapidly in several days.

CASE 7.—P. E., male, aged 11 years, was seen in consultation on June 5, 1939.

History.—A younger brother and sister, 8 and 5 years old, respectively, had fever, headache, and sore throat about eight days before, and were treated with neoprontosil. The patient began with the same symptoms on June 1, about the time the other children's illnesses were subsiding. He was given 10 grains of neoprontosil every four hours. He felt better next day or two, and the other children seemed well. The drug was discontinued for the other two children and was given to the patient irregularly and in very small doses for a day or two because he seemed all right. On the night before I saw him the fever rose again and a severe headache developed the following morning. Neoprontosil, 10 grains every four hours was prescribed again. He was nauseated and vomited several times this morning. Physical examination revealed a stiff neck, stiff back, a throat, swollen, red, acutely inflamed; ulcers on both sides

of pharynx; negative Kernig sign; photophobia, 1 plus; Brudzinski sign, 1 plus, active knee jerks; no paralysis. On June 5 spinal puncture showed 1,050 cells, 44 polymorphs, 56 lymphocytes; globulin, 2 plus; sugar, 1 plus. Culture was negative.

Treatment.—Neoprontosil was given, 15 grains every four hours for four days, with decreasing dosage for several days longer.

Progress.—The symptoms subsided rapidly after first 24 hours. Temperature normal on June 7, and the headache was much better and disappeared entirely in three or four days. The stiffness of the neck and back subsided in four or five days. There was no paralysis.

CASE 8.—J. W. P., male, aged 11 years, was admitted to the hospital on June 30, 1939, and discharged July 16, 1939. The illness began June 25 with a sore throat, headache, and fever of 102° F. He was seen at home June 27; the throat was congested, mucous membrane swollen and red, frontal headache present. Neoprontosil, 10 grains every four hours, was given. The temperature dropped to normal in 24 hours, and his mother stopped giving night doses thereafter, so that he got only 40 grains per day. On June 30 the temperature rose high again, headache became worse, and he complained of stiffness of the neck and pain on swallowing. Physical examination revealed pain on flexion of neck, stiffness in back and pain on flexion of back; normal, active knee jerks; moderate photophobia; congested throat; mucous membrane swollen, edematous; no paralysis. On June 30 spinal fluid contained 46 cells, with lymphocytes predominating; globulin, negative; sugar, slight trace. Wassermann and colloidal gold tests were negative.

Treatment.—Tablets of neoprontosil, 10 grains every four hours, were given from June 30 to July 5, 1939.

Progress.—On admission June 30 the temperature was 101° F.; it was normal July 1; it rose to 100° F. on July 2 and 3, and then it returned to normal. Symptoms subsided rapidly in a few days after admission. There was no paralytic involvement.

CASE 9.—F. L. C., Jr., male, aged 4 years, was admitted on July 14, 1939, and discharged to quarantine at home July 18. The illness began on the evening of July 11 with fever. When he was seen at home the next morning, he had fever and congestion of the pharynx. Neoprontosil, 5 grains every four hours, was prescribed. On the evening of July 13 the fever went higher again, and the child developed severe headache and became nauseated. This continued until he was seen on the morning of July 14. He complained of stomachache and mild pains in the arms. Physical examination revealed stiffness of neck and back, hyperactive knee jerks, negative Kernig sign, pupils in mid-dilation, no muscular weakness; however, he complained of pain in the left arm. The spinal fluid contained 80 cells, 56 polymorphs, 44 lymphocytes; no globulin, sugar, 2 plus, Wassermann and colloidal gold tests were negative, as was the culture.

Treatment consisted of neoprontosil, 2.5 per cent solution, 5 c.c. intramuscularly, repeated in four hours, then 5 grains every four hours by mouth.

Progress.—The temperature, 102° F. on admission on July 14, dropped to 98-99° F. on July 15. Stiffness in the back and the neck subsided in three or four days. He was discharged July 18 to quarantine at home. There was no paralytic involvement.

CASE 10.—J. R., female, aged 3 years, was admitted to the hospital on July 23, and discharged Aug. 13, 1939. The child began complaining of headache and sore throat, and had a fever on July 22. This persisted, and she became irritable, stayed in bed and did not want to be disturbed. There was no nausea or vomiting. (Patient lives in same apartment house with child now in the hospital with poliomyelitis [paralysis].) Physical examination showed acutely inflamed throat, stiff neck and

spine, some retraction of the neck, pain on sitting up, hyperactive knee jerks, no paralysis. On July 23 the spinal fluid contained 235 cells, 3 polymorphs, 97 lymphocytes; globulin, 2 plus; sugar, 1 plus, Wassermann and colloidal gold tests were negative.

Treatment.—Neoprontosil solution 2.5 per cent, 5 c.c. every four hours, was given intramuscularly for three injections. Neoprontosil in tablets, 5 grains every four hours, was given until July 29.

Progress.—The temperature dropped from 103° F. on admission July 23 to 100-101° F. on the next day, and to 99° in the afternoon of July 25. Neck and back were still stiff on July 30, but her general condition was much better, and all symptoms rapidly subsided following this. There was no paralytic involvement.

CASE 11.—W. Von M., male, aged 1 year, was admitted to the hospital Aug. 1, 1939, and discharged Aug. 21, 1939. On July 30 the illness began with high fever and vomiting. The fever persisted, and the mother noticed stiffness of back the next day. On physical examination the neck was not stiff, but the baby seemed in pain when handled, especially when his back was bent. He had marked upper respiratory infection, loose cough, mucous râles (coarse) over chest. The throat was red, with swollen, edematous mucous membrane, giving the appearance of a membrane in upper posterior nasopharynx. He was given 20,000 units of diphtheria antitoxin after first spinal puncture on August 1 was negative. Throat culture and smear were negative for diphtheria organisms. On August 1 the spinal fluid contained 2 cells, no globulin, and sugar, 1 plus. The following day spinal puncture showed 17 cells, with lymphocytes predominating; globulin, 1 plus; sugar, 1 plus; Wassermann, negative; colloidal gold curve, negative; culture, negative.

Treatment.—Neoprontosil, 2½ grains every three hours from Aug. 1 to 5, 1939, then every four hours until August 9.

Progress.—Movement of the head and the back caused pain until August 6. From 102.5° F. on admission on August 1, the temperature went to 105° F. the next day and dropped to normal on August 3. There was no paralytic involvement.

CASE 12.—B. S., female, aged 21 years, admitted to the hospital on Aug. 8, 1939, was seen in consultation. The illness began about 11 P.M. August 7 with a headache. She had been indiscreet in eating earlier in the evening. At 3 A.M. August 8 she became nauseated and vomited. A few hours later, after an enema, she felt better. However, the headache persisted, and through the day the temperature rose above 101° F. This afternoon she noticed a little stiffness of the neck and pain on flexion. Physical examination revealed slight stiffness of the neck and pain in lower back when neck is flexed; congestion of throat and areas of redness and edema on pharynx. No Kernig sign was elicited; Brudzinski sign was suggestive; knee jerks were active. On August 8 spinal fluid was clear, with 182 cells, 20 polymorphs, 80 lymphocytes; globulin, 1 plus; sugar, 1 plus; Wassermann, negative; colloidal gold curve, negative.

Treatment.—Neoprontosil tablets, 20 grains every four hours, were given until August 12, 15 grains until August 14, then 10 grains until evening of August 15.

Progress.—The temperature of 99.8° F. on admission dropped to normal in next few hours. Headache and stiffness in neck and back subsided in three or four days. No paralytic involvement.

CASE 13.—J. M. E., Jr., male, aged 3½ years, was admitted Aug. 10, and discharged Aug. 30, 1939. The illness began August 9 with headache, fever, and sore throat. He was seen at home and was given neoprontosil, 5 grains every four hours. The day of admission he complained of a sore throat, headache, and pain on motion of head and back, and he had more fever. Physical examination disclosed an inflamed throat, edematous patches on pharynx and tonsils, stiff neck and back (resistance to bending because of pain), knee jerks present on both sides, no Brudzinski

or Kernig sign, and no paralysis. Because the child moved and struggled traumatic, bloody spinal fluid was obtained on August 10 and 11. *Spinal puncture* on August 12 under anesthesia, showed clear fluid, 146 cells, 80 polymorphs, 20 lymphocytes; globulin, 1 plus; sugar, 1 plus; Wassermann, negative; culture, negative. The blood Wassermann test was also negative.

Treatment.—Neoprontosil, 5 grains every four hours, was administered until August 16.

Progress.—The temperature varied as follows: from 104° F. on admission, August 10, to normal on August 11; to 101° F. again in the afternoon; on August 13, 103° F.; on August 14, 103° F., and daily rise until August 17. Stiffness of the neck and back subsided by August 12. The spleen was easily palpable, firm on August 15. No malarial parasites were found in thick and thin smears on August 11, 15, and 16. In a concentrated blood examination on August 17, *Plasmodium vivax* was found. He was given atabrine, ¾ grain three times a day. The temperature was normal on August 18. Malarial infection was apparently coincidental to poliomyelitis. (Meningeal symptoms subsided before treatment for malaria, and simple tertian infection is not likely to give cerebral symptoms.) There was no paralytic involvement.

CASE 14.—A. B., female, aged 4 years, was admitted to the hospital on Aug. 12, 1939, and discharged Aug. 21, 1939. Illness began August 9 with fever and stiffness of neck, which persisted until admission. (Patient has brother with poliomyelitis in hospital at present, paralyzed since July 29.) The patient became nauseated August 11 and vomited everything taken until admission. She was given neoprontosil 5 grains every four hours at home for past three days. Physical examination revealed stiff neck and back, painful on flexion; red throat, congested edematous appearance; hyperactive knee jerks; Kernig sign, negative; Brudzinski sign, slightly positive; and no paralysis. On August 12 the spinal fluid contained 70 cells, 70 polymorphs, 30 lymphocytes; globulin, 1 plus; sugar, 1 plus. Colloidal gold curve was negative, and culture was negative.

Treatment.—Neoprontosil, 7½ grains every four hours, was given until August 18. Because of dehydration from vomiting she was given 300 c.c. of a 5 per cent glucose solution intravenously on admission.

Progress.—Vomiting ceased after admission to the hospital. The temperature decreased from 100° F. on August 12 to normal on August 14. The stiffness of the neck and back subsided by August 16. Convalescence was uneventful. There was no paralytic involvement.

In addition to the reported nonparalytic cases, during the epidemic eight other children were seen with varying combinations of severe headache, sore throat, fever, and vomiting, all having some stiffness of the neck and back, of a degree comparable with most of those reported. For economic or other reasons, they were not sent to the hospital, and spinal puncture was not performed at home. They were all treated with neoprontosil, as above, and the illness subsided in all promptly without paralytic involvement. These cases were not reported as poliomyelitis because spinal puncture was not made to confirm the diagnosis. Clinically, during an epidemic of poliomyelitis, I consider them as positive cases of poliomyelitis, and they were kept in quarantine for the usual period of three weeks.

DISCUSSION

Kelson[3] in 1937 and Toomey and Takacs[4] in 1938, as the result of their experiments, concluded that sulfanilamide "does not modify the

course of experimental poliomyelitis in monkeys." In September, 1937, Rosenthal, Wooley and Bauer,[5] gave the first suggestion that prontosil was effective in preventing the development of a virus disease, experimental choriomeningitis in mice. These animals were experimentally infected and treated shortly thereafter with the drug. With the 1:100,000 dilution of the virus, 55 per cent of the controls and only 5 per cent of the treated mice died. These investigators found prontosil alone was effective with the virus of choriomeningitis. Prontosil soluble and prontylin (sulfanilamide) were inactive. McKinley, Meek, and Acree,[6] using more concentrated suspensions of virus and larger dosage, failed to confirm these experiments and failed to find prontylin, prontosil or sodium sulfanilyl sulfanilate of value in prevention or treatment of several other experimental virus infections.

In the *Proceedings of the Staff Meetings of the Mayo Clinic,* August 2, 1939, experiments are presented which tend to show that sulfapyridine, "not only did not prevent poliomyelitis (experimental) but seemed to have an additive neurotoxic effect. The period of incubation was shortened, paralysis progressed more rapidly, the symptoms were more pronounced, death occurred earlier, and the lesions of the spinal cord and brain were more destructive and more extensive than in the control animals. Moreover, sulfapyridine did not prevent the growth of the associated streptococcus." They conclude as a result of these experiments, and of those quoted above, that "sulfapyridine and sulfanilamide are contra-indicated in the treatment of poliomyelitis in human beings."

This latter report has been received as my clinical experiment with neoprontosil is nearing its end. The experiments with sulfapyridine would seem to lead to the conclusion arrived at, that this drug was contraindicated in the treatment of human poliomyelitis. The other animal experiments with sulfanilamide and prontosil did not prompt the use of the word "contraindicated," as used in the report from the Mayo Clinic. These other investigators concluded that sulfanilamide was "without value in the treatment or prevention of experimental poliomyelitis," and the report on prontosil was conflicting in regard to experimental choriomeningitis in mice, a virus disease. Rosenthal, Wooley, and Bauer obtained rather striking results in this disease with prontosil and failed to obtain similar results in the same experiments with prontosil soluble and prontylin (sulfanilamide). This would seem to suggest that perhaps the diazo linkage in prontosil might be of some importance in inhibiting this virus infection under the conditions imposed by the experiment. In a discussion of the use of sulfanilamide and related compounds by Alex E. Brown,[7] the opinion is reached that "in spite of an accumulation of opinions to the contrary, it still seems likely that neoprontosil may possess some in-

dependent action due to the intact neoprontosil molecule, or to some split product of this molecule rather than sulfanilamide."

The clinical experiments with neoprontosil in an epidemic of serious proportions in the city and county of Charleston, S. C., seem to indicate that this drug may, likewise, have an inhibiting effect on the virus of poliomyelitis in the human host. No reference could be found to the use of neoprontosil in experimental poliomyelitis in monkeys. In view of the suggestive report of Rosenthal, Wooley, and Bauer, and of my clinical experience in this epidemic, it might be of interest to conduct experiments with this drug in animal poliomyelitis, as with sulfanilamide.

Further clinical reports on its use in prevention and treatment of poliomyelitis are needed. Under similar circumstances, in an epidemic of poliomyelitis, its use for this purpose would seem to be justified on the basis of this report. Certainly, there was nothing in my experience with this drug to indicate any contraindication to its use in poliomyelitis in human beings. I realize that poliomyelitis is a disease in which it is difficult to draw conclusions from a relatively small number of cases, but, on the whole, the apparent results were rather striking, and it is difficult to avoid the feeling that the drug is clinically effective in inhibiting the virus of poliomyelitis.

SUMMARY

1. There is no way of making a diagnosis of poliomyelitis in the absence of involvement of the central nervous system. In an attempt to determine its possible prophylactic and therapeutic value in clinical poliomyelitis, neoprontosil was given to 440 acutely ill children, during an epidemic of poliomyelitis, in approximate dosage of 1 grain per pound of body weight per day.

A. Of these children, only one developed paralysis. This was a transient paralysis developing on the fifth day of illness in a child whose mother had not kept up the maintenance dose of the drug. Symptoms subsided when full dosage was resumed, and paralytic involvement had completely subsided in the three-week period of quarantine.

B. Two other children developed meningeal symptoms on the fifth day of illness, under similar circumstances (noncontinuance of the maintenance dose). These symptoms subsided without paralysis with resumption of full dosage of the drug.

2. A. Fourteen cases of poliomyelitis are reported in which neoprontosil was given in the preparalytic stage. Of these, only one, the patient referred to above, developed paralysis. In this child the maintenance dose was not kept up, and the involvement, occurring on the fifth day of illness, was transitory (less than three weeks).

B. Eight cases in which a clinical diagnosis of meningeal involvement of poliomyelitis was made subsided with neoprontosil medication without paralysis. They were not reported as positive cases because they were not confirmed by spinal fluid examination.

3. Eleven patients with paralytic involvement were treated during this time by administration of neoprontosil as above. Toxic symptoms subsided in this group within twenty-four to forty-eight hours, and there was no apparent advance in paralytic involvement after the adequate dosage of the drug was reached and held for twenty-four to forty-eight hours. There were no deaths in the acute phase of the disease. However, there were included in this series two acute fulminating cases with practically complete involvement of all extremities and respiratory musculature, necessitating the use of the respirator. One of these patients died two months later, while convalescing and recovering some respiratory function. Death was caused apparently by an attack of asthma, from which she had suffered for several years.

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SPONTANEOUS ERECTIONS IN EARLY CHILDHOOD

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FEW writers have expressed themselves about the incidence in children of penile erections not associated with masturbation. Even general statements or opinions are rarely to be found in the literature, which abounds in discussions of the structure and function of the erectile tissues. Debierre, who gave detailed accounts concerning erections in man, animals, and even plants, failed to record their occurrence in small boys.[1] Moll said summarily: "Erections occur during childhood; they have been observed even in infancy." He mentioned as possible causes external irritations resulting from strictured prepuce or balanitis, distention of the full bladder, and "internal stimuli connected with the development of the genital organs, and more especially that of the testicles." He considered infantile erections as being nonsexual in character, even though there is nothing in their appearance to distinguish them from sexual erections.[2] Pouillet asserted that all boys have the faculty of erections in quite early childhood; he reported that, if the edge of a child's foreskin is tickled with a feather, the penis swells up and becomes erect and the infant grasps at it with his hands.[3] Freud, for all his preoccupations with infantile sexuality, had nothing to say about spontaneous penile erections in small children.

In conjunction with a study of the development of sex awareness of children, the parents were asked whether erections had ever been noticed in their boys, and, if so, data were obtained about the ages at which they began, the circumstances under which they occurred, and the time until which they continued to appear. No point was made of the frequency of their incidence, since any statements to that effect would refer to the frequency of observation rather than that of actual occurrence. Most mothers were surprisingly definite in their affirmations or negations. As they changed diapers, bathed their sons, took them to the toilet, dressed and undressed them, the presence or absence of erections could not very well have escaped their attention. Sexual significance was not attached to them by any of the parents. Even those mothers who displayed embarrassment when talking about any other sex topic spoke freely about early erections in their boys.

Spontaneous erections were seen in 47 (36.7 per cent) of the 128 boys of the study series. The ages at the time of first observation by the parents (which, of course, are not always the ages of real onset)

This presentation is one of a series resulting from a study of the development of sex awareness in children. This study was supported by a grant from Child Neurology Research (Friedsam Foundation).

were ascertained for forty-five of the children. In two boys (6 and 7 years old), not even the approximate time of first notice could be elicited. Not less than thirty-eight boys were reported as beginning to have erections during the first five years of life, and only seven in the course of the second half of the decade. This may in part be due to the greater intimacy between mother and child and hence better opportunity for mothers to perceive such transient changes during the preschool age of their offspring. The earliest observation was traced to 2 months of age; two children began having erections at about 6 months, and seven began in the second half of the first year.

TABLE I

ONSET OF SPONTANEOUS ERECTIONS

AGE WHEN FIRST NOTICED	NUMBER	PER CENT
Before 1 year	10	21.3
1 yr.	8	17.0
2 yr.	3	6.3
3 yr.	6	12.8
4 yr.	6	12.8
5 yr.	5	10.6
6 yr.	2	4.3
7 yr.	3	6.3
8 yr.	0	0
9 yr.	0	0
10 yr.	2	4.3
Not stated	2	4.3
Total	47	100.0

Of the forty-seven boys, twelve (25.5 per cent) were known to have erections for a limited period of time only. All others, 74.5 per cent of the group, continued having them up to the time of the investigation. The temporary erections in the children of the first group occurred without exception in the age range between 3 and 6 years. They were noticed at 3 years of age in two boys; at 3 and 4 years, in one boy; at 4 years, in three boys; at 4 and 5 years, in two boys; at 5 years, in one boy; at 5 and 6 years, in one boy; at 6 years, in two boys.

The age distribution of the thirty-five boys who were still having erections at the time of the inquiry is shown in Table II.

TABLE II

AGE AT TIME OF INQUIRY (YEARS)	NUMBER HAVING SPONTANEOUS ERECTIONS
5	8
6	5
7	5
8	4
9	7
10	3
11	3
Total	35 (74.5%)

The circumstances under which spontaneous erections were observed were reported by the parents of thirteen of the boys. Coincidence with fullness of the bladder upon awaking in the morning or associated with urinary urges was remarked upon by ten mothers. One woman stated that, whenever she saw that her 6-year-old son had an erection, she told him to go to the toilet, "and after he goes he is all right." One father noticed erections in his son while he was being bathed, another saw them for a period of two years in his boy during sleep since the age of 7 years. In this connection it is interesting to refer to a statement made by Moll to the effect that matutinal erections of a nonsexual nature may also occur in adults, due "to distention of the bladder, which is supposed by reflex action to lead to distention of the corpora cavernosa of the penis. It is certain, at any rate, that these matutinal erections are not caused by sexual thoughts, nor as a rule do they induce sexual feelings."[2] In fact, there was only one child in the whole series, a 6-year-old boy, in whose erections sex preoccupations may have played a significant part. The child had, at the age of 5 years been induced to sex play by a girl in the neighborhood, and since those experiences the mother observed frequent erections which she had not seen before.

Few children have ventured to express themselves about their spontaneous erections. One boy, at 5 years, asked his mother what they meant and what caused them. She reported in retrospect: "I told him that was a natural thing. That seemed to satisfy him." Another boy, at 6 years, upon awaking in the morning, wanted to know "why his yitty [term for penis] was like that [erect]." The mother of a 6-year-old boy reported him as pointing often to his erect penis and saying: "Mamma, look at me!" A 7-year-old said to his mother: "Look at this, how stiff this is getting!" She replied: "Don't pay attention to it." A 10-year-old boy, speaking of his erections which he had had for the past two or three years, said: "It just happens." He did not connect any sexual fantasies with them.

No correlations could be established between the erections and inflammatory or other penile disorders.

The average intelligence quotient for the group was 94. The I.Q. distribution was as follows:

I.Q.	NUMBER
71- 80	5
81- 90	11
91-100	12
101-110	14
111-120	4
121-130	0
131-140	1
Total	47

Of the forty-seven boys in whom spontaneous erections were observed, nineteen (40.4 per cent) also had histories of masturbation in the past or at the time of the inquiry. In the remaining twenty-eight (59.6 per cent), the presence at any time of masturbatory practices could not be elicited.

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TREATMENT OF ACUTE ALCOHOLISM WITH INSULIN

Report of a Case

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WE REPORT here one case of acute ethyl alcoholism in a child, which is of interest because of the high blood alcohol concentration and because of the uneventful recovery after the administration of glucose and insulin.

Numerous investigators have reported the interrelationship of the effects of ethyl alcohol on carbohydrate metabolism and of insulin in the treatment of experimental alcoholemia. Lundsgaard[1] has shown that the oxidation of ethyl alcohol is a specific liver function and that it does not take place in the muscle. The oxidation of the alcohol by the liver is an incomplete one and leads to the formation of an organic (acetic) acid. Salant,[2] working with rabbits, has shown that alcohol facilitates the removal of hepatic glycogen. Apparently, however, glycogen metabolism is not affected during profound alcoholic narcosis. Widmark[3, 4] has claimed that neither carbohydrate nor fat ingestion has any marked effect upon the disappearance of alcohol from the blood, but that it is increased by proteins. He later reports that insulin does strongly activate alcohol metabolism in dogs, doubling it in 200 minutes. Dogs with very active alcohol metabolism are apparently not affected. Erwteman and Heeres,[5] working with human beings, have shown altered blood alcohol tolerance curves in both acute and chronic liver damage and in diabetes.

Haggard and Greenberg[6] report that the toxicity of alcohol is inversely proportional to the level of the blood sugar in rats. When the blood sugar is 70 mg. per cent, the lethal concentration of alcohol in the blood is 8.0 mg. per cubic centimeter. When the blood sugar is 100 mg. per cent, the lethal alcohol concentration is 20 per cent higher. The modifying effects of the blood sugar level are apparently connected with the combustion of alcohol in the tissues. Bickel[7] has shown that in rabbits the utilization of alcohol by the organism is a function of the concentration of blood sugar and is affected by insulin. Clark, Morrissey, and Fazekas,[8] working with severe diabetes produced by pancreatectomy in cats, showed that oxidation of alcohol by excised liver suspended in saline is inhibited in diabetes and promoted by the addition of insulin. Other investigators (Serrianni,[9] Siegmund and Flohr,[10] Newman and Cutting,[11] and Sebastianelli[12]) have also shown that insulin promotes the oxidation and removal of alcohol from the

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blood. Lang and Schlick[13] claim that insulin does not aid in the removal of alcohol from the blood of dogs. Junge[14] reports that insulin hastens sobering but does not affect the blood alcohol content. Hirschfelder and Maxwell[15] claim that insulin has no effect upon the rate of oxidation or upon the toxic effects of alcohol in rabbits.

Clark and Gibson[16] report the successful treatment of acute methyl alcoholism in dogs with sodium bicarbonate, glucose, and insulin. Clark and Morrissey[17] have applied this treatment to acute ethyl alcoholism in dogs and report that neither glucose, sodium bicarbonate, nor sodium citrate increased the rate of disappearance of alcohol from the blood, but that when insulin is administered simultaneously with the above substances the rate of disappearance of the ethyl alcohol is increased. Such animals were apparently in better condition during the experiment and appeared to recover completely sooner than those in the other groups. They conclude that insulin catalyzes the oxidation of ethyl alcohol.

Widmark[18] reports that the lethal alcohol concentration in the blood in adult man is 500 mg. per cent and that a total dose of from 11 to 14 Gm. of alcohol may be fatal for children in the first year of life. The British Royal Commission has set a blood alcohol concentration of 700 mg. per cent as the lethal concentration for man.

CASE REPORT

A. B., a 3 year and 9 month old colored male, was admitted to the Duke Hospital on March 10, 1939. The family and past history was negative. At approximately 10 A.M. on the day of admission the child drank one-half pint (about 200 c.c.) of rubbing alcohol (70 per cent). He soon vomited a small amount, became very drowsy, and then passed into coma. At about 2 P.M. he was brought to Duke Hospital where emergency treatment consisted of gastric lavage and leaving about 150 c.c. of tap water in the stomach. About one hour later he was given 200 c.c. of strong coffee by stomach tube and 150 c.c. of 10 per cent glucose intravenously. As he did not respond, he was admitted to the ward at 4:30 P.M. Physical examination on admission revealed a comatose negro child who had a strong alcoholic breath, a temperature of 37.7° C. (99.9° F.), pulse 120, respiration 26, and blood pressure 96/60. The pupils were small, almost pin-point, but reacted sluggishly to light. The heart and lungs were clear, the muscles hypotonic, and the knee jerks absent. The gag reflex was sluggish. After being admitted to the ward the patient was given 150 c.c. of 10 per cent glucose intravenously and 10 units of insulin intramuscularly at 9:50 P.M. He responded somewhat to this treatment and was conscious for the first time since admission. He was given 0.5 c.c. of coramine intramuscularly at 9:55 P.M. and immediately became very restless, but was conscious and asked for water to drink.

The child's temperature reached 40.5° C. (104.9° F.) at midnight. He was given an alcohol sponge bath, and the temperature gradually returned to normal during the next twelve hours. He complained of slight pain in the epigastrium, but no headache or other disturbances. He was not nauseated, nor did he vomit at any time during the hospital stay. He was discharged on March 13, 1939, three days after admission.

The following blood and urine analyses were performed:

2:00 P.M.	3/10/39	384 mg. % alcohol (blood)
2:30 P.M.	3/10/39	198 mg. % alcohol (urine)
10:00 A.M.	3/11/39	15 mg. % alcohol (blood)

Coramine was given to this patient very shortly after the administration of insulin and glucose. Its administration was probably unnecessary as the respiration was satisfactory. Working in this laboratory, McCrea and Taylor[19] have shown metrazol to be an excellent respiratory stimulant in acute alcoholism in which respiration has almost stopped but in which the heart is still beating.

SUMMARY

A review is given of the literature on the effect of insulin and glucose on the rate of disappearance of alcohol from the blood stream.

A case of acute alcoholism in a child, which from all indications would have been fatal, was successfully treated with insulin and glucose.

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TREATMENT OF TETANY OF THE NEWBORN INFANT WITH DIHYDROTACHYSTEROL

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TETANY of the newborn infant was described first by Kehrer[1] in 1913. Shannon[2] and Bass and Karelitz[3] renewed interest in this subject in 1931, and since this date a number of reports have appeared.[4]

The treatment of tetany seen in the newborn infant in the past has consisted of the use of calcium, vitamin D, parathyroid extract, and the giving of a milk, such as breast milk, which is low in phosphorus content. With the introduction of dihydrotachysterol by Holz, Gissel, and Rossman,[5] a drug has been made available that seems ideal for use in tetany of the newborn infant believed due to hypoparathyroid activity. The plan of treatment used in an infant developing tetany considered due to hypoparathyroidism during the first few days of life will be given.

W. T. B., a white male infant, was born at St. Joseph's Infirmary May 10, 1939. He was the second male child of American parents. The mother had been instructed to take three capsules of navitol each day and 45 gr. of dicalcium phosphate daily during gestation, but this regime was not carried out in full. At seven months the mother threatened to go into labor and was hospitalized. The infant was delivered at eight and one-half months and weighed 5 pounds 8 ounces at birth.

When the infant first was observed in the hospital, he appeared normal in every respect. Five per cent glucose and water, together with breast feedings, were started. After one week the mother had insufficient milk, so supplementary feedings of a powdered milk were given. The infant remained in the hospital until he was 3 weeks of age and developed normally. Oleum percomorphum was started during this period. Approximately a week after being taken home the infant was noticed to be nervous, and the mother stated that he was having attacks of twitching. At the same time he developed loose stools with some blood in the movements. He was seen at this time and found to have temperature of 100.4° F., a positive Chvostek's sign, hyperactive reflexes, and the stools contained considerable mucus and blood.

The infant was given whole blood intramuscularly, and extra breast milk was obtained for the supplementary feedings. He continued to be very "jumpy," as the mother described it, and she became alarmed when he developed choking spells. During these spells he became quite cyanotic. A specimen of blood was taken at this period, and the calcium was found to be 5.4 mg. per 100 c.c., and the phosphorus, 6.2 mg. Fifteen drops of viosterol were given daily, and 12 Gm. calcium gluconate were added to the milk. The infant made no improvement. X-ray study of the chest revealed no abnormality. Five days after starting the viosterol and calcium gluconate, another calcium and phosphorus determination was made. The calcium at this time was 4.7 mg., and the phosphorus, 4.8 mg.

The urine was tested with Sulkowitch's reagent,* and no calcium was found. Dihydrotachysterol was started at this time, the infant receiving 5 drops three times daily. Urine tests were made several times daily for calcium, and for three days there was no precipitate. The dosage was increased to 10 drops three times a day, at which level it was maintained for five days with no precipitation in the

*2.5 Gm. of oxalic acid, 2.5 mg. of ammonium oxalate, and 5 c.c. of glacial acetic acid are dissolved in distilled water and made up to a volume of 150 c.c. Equal amounts of the reagent, when added to urine, precipitate the calcium present as a fine white cloud of calcium oxalate.

urine with the Sulkowitch reagent. The blood calcium at this time was 6.4 mg., and the phosphorus, 5.7 mg.

The dosage of dihydrotachysterol was increased to 15 drops three times daily, and in twelve hours the urine showed a very slight cloudiness on testing. For the first time the infant began to improve, was less nervous, and did not choke, as the mother described it. Another blood calcium study was made four days after the increase in dosage of the dihydrotachysterol, and the calcium was found to be 11.4 mg., and phosphorus, 4.5 mg., per 100 c.c.

As the urine began to show a heavier precipitate of calcium, the dihydrotachysterol was decreased to 5 drops three times daily. In two days the infant began to have choking spells which were not as severe as the original ones. The Sulkowitch test at this time showed a very faint cloudiness. The dosage of the dihydrotachysterol was increased to 10 drops three times daily, and the urine became more cloudy. After four days the dihydrotachysterol was decreased one drop three times daily. The urine continued to be slightly cloudy on testing for calcium.

The infant has continued to do well since the dihydrotachysterol was discontinued. The calcium and viosterol have been continued. An x-ray examination of the bones of the wrist at 3 months of age showed no abnormality in calcification.

COMMENT

Yanase[6] was the first to suggest that tetany in infants might be related to parathyroid tetany, and he was able to demonstrate hemorrhages in the parathyroids in a considerable number of newborn infants. However, no changes in the parathyroid glands of an infant with tetany were seen by Guild[4a] at autopsy.

Bakwin and Bakwin[7] called attention to the fact that another factor, other than hemorrhages into the parathyroids, might be responsible for the lowered calcium and increased phosphorus content in the blood of some infants with tetany. They showed that there occurs a physiologic fall in the serum calcium and increase in the phosphorus, the maximum occurring between the third and fifth days of life. They suggest that, inasmuch as there has been shown to be a histologic hyperactivity of the maternal parathyroid glands,[8] the parathyroid activity in the fetus possibly is held in abeyance in response to the maternal overactivity.

There is also other evidence that this type of tetany is caused by retarded parathyroid activity. Greenwald[9] and Schilling[10] stress that one of the striking features of hypoparathyroidism is the reduction of the output of phosphorus in the urine. Schloss and Crawford[11] found that the amount of phosphorus in the urine of the newborn infant fell during the second three days of life and then increased slightly the third three days, but never reached the initial value.

Since vitamin D[12] apparently has no effect upon the blood calcium and phosphorus in this group of infants and in light of the above studies, it is more than probable that the tetany seen in infants with a lowered calcium and increased phosphorus in the blood serum and with no calcium being excreted in the urine is of parathyroid origin.

Albright[13] recently outlined a method of management of hypopara-

thyroidism, using dihydrotachysterol to increase the absorption of calcium from the intestinal tract, and observing the excretion of calcium through the urine by means of the Sulkowitch reagent. Dihydrotachysterol, a fraction of irradiated ergosterol, increases the absorption of calcium from the intestinal tract and also aids in the excretion of phosphorus in the urine.[14]

Albright[13] points out that the serum calcium level in a normal person is from 9.5 mg. to 11 mg. per 100 c.c., and in a completely parathyroidectomized person, from 5 mg. to 7 mg. The normal level of blood calcium is above the threshold for the excretion of calcium in the urine, this threshold varying between 7.5 mg. and 9 mg. Calcium can be precipitated in the urine by means of the Sulkowitch reagent which contains the oxalate radicals buffered at such a pH that, when equal amounts of the reagent are added to urine, the calcium will be precipitated as a fine white cloud of calcium oxalate. Albright states that, if there is no precipitate, there is no calcium being excreted, and that the serum calcium is probably from 5 mg. to 7.5 mg. per 100 c.c. Should the test show a fine white cloud, there is a moderate amount of calcium, and the level of calcium in the serum is satisfactory. When the precipitate looks like milk, there is danger of hypercalcemia.

Large doses of dihydrotachysterol, 15 drops three times daily, were necessary to raise the calcium in this infant and to start its excretion in the urine. No unusual symptoms due to the large doses were noticed, and x-ray examination of the bones at 3 months of age showed no abnormality.

SUMMARY

The case of an infant believed to have parathyroid tetany and treated with dihydrotachysterol is reported.

The method of treatment with dihydrotachysterol and the use of the Sulkowitch reagent are presented.

Large doses of dihydrotachysterol were necessary to control the tetany. No harmful results arising from the necessary use of large amounts of this drug over a long period of time were noted.

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PNEUMOCOCCAL MENINGITIS

With Report of Sulfapyridine Reaction Involving Mucous Membranes

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IN reviewing the literature on pneumococcal meningitis it is encouraging to find the recent decrease in the mortality rate, and it is interesting to note that this sudden drop parallels the introduction of sulfanilamide and sulfapyridine into medical therapeutics. Before 1937 it was the exceptional case which recovered from meningitis due to the pneumococcus. Hewell and Mitchell[1] reviewed the cases from 1927 to 1937 occurring at the Children's Hospital of Cincinnati and the Cincinnati General Hospital and reported the mortality rate to be 100 per cent. Recently there have been four papers[2-5] reporting recoveries following sulfapyridine therapy.

We are reporting this case of Type XVIII pneumococcal meningitis, not merely because of the recovery, but because of a new and unusual complication which arose while the child was in the hospital.

A white boy, aged 5 years, was admitted to Children's Hospital on April 20, 1939. The history revealed that the child had always been well, even to the extent of escaping all of the infectious childhood diseases. Two days before admission, on April 18, the patient developed a fever of from 101° F. to 102° F. (38.8° C.), vomited, and appeared to have a cold. The following day a doctor saw the child, but there were no positive physical findings. About 2:00 A.M. on April 20, the boy became unconscious, and the mother noticed that the right eye was turning out and that the right eyelid drooped. At 8:00 A.M. the doctor again saw the child, and on finding a stiff neck and a positive Kernig sign, sent the child to the hospital.

Physical examination revealed an acutely ill, unconscious child with a ptosis of the right eyelid. The skin was pale and dry with no eruptions. The cervical nodes and a right postauricular node were slightly enlarged. The right eye was closed and appeared to be slightly edematous. The right pupil was markedly dilated, the left was constricted, and neither reacted to light. The right eye was turned out. The tympanic membranes were normal. The palate and pharynx were injected, and the tonsils were slightly enlarged and inflamed. The breath sounds were normal. There was a soft systolic murmur heard best at the left of the sternum in the fourth interspace. The abdomen was normal. Examination revealed a stiff neck and spine without opisthotonos and with a markedly positive Kernig sign. The remaining reflexes were normal. Temperature was 102.2° F. (39° C.); pulse, 104; respirations, 32.

A lumbar puncture gave a milky fluid under increased pressure. Laboratory report on this fluid was as follows: Cloudy fluid loaded with Type XVIII pneumococci; no sugar; cells 747, chiefly polymorphonuclears; blood count, 19,000 white blood cells with 94 per cent polymorphonuclears.

Course in Hospital.—A duodenal tube was inserted, and sulfapyridine was started. The initial dose was 45 grains (3 gm.), followed by 15 grains (1 gm.) every four

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hours. The child was given concentrated feedings and subcutaneous fluids. His condition grew steadily worse so a second lumbar puncture was done that evening. On April 21, the spinal fluid cell count was 3,280. Intravenous sulfapyridine was started, and 60 grains (4 gm.) were given by vein in addition to 90 grains (6 gm.) by mouth. Also 120,000 units of specific pneumococcal rabbit serum was administered intravenously. The child's condition remained critical. Temperature was 100.5° F. (38° C.), with a pulse of 140. On April 22 the spinal fluid cell count was 2,322, and the organisms which had been extracellular were all intracellular. The blood sulfapyridine concentration was 16.6 mg. Thirty grains (2 gm.) of sulfapyridine were given by vein and 90 grains (6 gm.) by mouth. On the third day the spinal fluid showed 1,280 cells with a negative culture. The urine was showing numerous red blood cells, presumably due to the medication. The concentration in the blood had dropped to 7.5 mg. so the dosage by mouth was increased to 105 grains (7 gm.) of sulfapyridine. No infection had appeared in either the chest or ears.

By the seventh day the spinal fluid was clear, and the cell count was 48, the sugar was 58 mg. About the same dosage of sulfapyridine had been given daily, but the blood concentrations fell to between a trace and 3 mg. The child had regained consciousness, and clinically he was improved. After the phleboclysis had run for a week, the cannula was removed, but the oral administration of the drug was continued. Regardless of the amount given, the concentration showed no increase in the blood. An x-ray of the sinuses showed cloudiness of the ethmoids, but this was probably due to the irritation caused by the duodenal tube which remained in the nose for seven days. On the ninth day it was noticed that the child was deaf, in contrast to hearing well the first few days of consciousness. The pupils remained unequal in size but both reacted to light. The third and fourth cranial nerve paralysis persisted in the right eye. On May fifth, the sulfapyridine was discontinued, a total of 1740 grains (113 gm.) having been given over a period of fifteen days. Twelve hours after the drug was stopped, a morbilliform rash appeared on the face and within forty-eight hours had spread over the entire body.

Coincident with the development of the rash on the skin, a heavy, bluish white, gelatinoid membrane appeared on the lips, buccal mucous membranes, and gums, completely covering all of these structures including the pharyngeal mucosa. The mucous membranes of the nose and the conjunctiva were similarly involved, but to a lesser degree. The appearance of the membranes closely resembled the pseudomembrane seen after the application of an escharotic, such as an acid, to the mucous membranes. No treatment other than peroxide and a mild mouthwash was used, and the membrane gradually disappeared, leaving a bright red surface. The clearing of all of the mucous membranes paralleled the disappearance of the morbilliform rash in the course of six days. We feel safe, therefore, in assuming that the involvement of both skin and mucous membranes was an exhibition of the toxic effect of sulfapyridine.

On May 10, the hearing returned. During this time the paralysis of the right eye muscles was gradually clearing. The patient complained of double vision, but at the time of discharge on June 6, the function of all the eye muscles had returned except in the inferior oblique and the superior rectus muscles. Dr. Leonard Swigert, staff ophthalmologist, has followed this eye complication. The last spinal fluid showed a cell count of 22 with normal protein and sugar. Except for the slight paresis of the right eye, the patient appeared to have made a complete recovery from the pneumococcal meningitis and the complications.

COMMENT

The study of this case brings out several interesting observations. First, previous to the onset of the meningitis there was no history of a

draining ear or pneumonia, and during the course of the disease the blood culture remained negative. Second, despite the fact that huge doses of sulfapyridine were administered, the concentration of the drug in the blood could not be maintained at the desired level of 10 to 15 mg. It is quite possible that the medicine by mouth was not absorbed in the intestine but was lost in the feces. Third, Long[6] states that the toxic manifestations of sulfapyridine are essentially those observed in sulfanilamide therapy. These are nausea, vomiting, dizziness, headache, fever, morbilliform rashes, tingling of the extremities, and blood dyscrasias. In this case the morbilliform rash was present, complicated by the extensive involvement of the mucous membranes. We believe this to be a manifestation not previously reported in the literature.

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SARCOMA OF THE VULVA IN A SEVEN-MONTH-OLD INFANT

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SARCOMA of the vulva is a rare disease, and it is still more unusual to find it occurring in children. In eighteen cases collected by Bell,[1] only one was in a child, five were in women from 18 to 30 years of age, and the rest were in older women. Abt[2] does not discuss sarcoma of the vulva but, in referring to sarcoma of the vagina, says that it occurs more frequently in childhood than in adult life. Veit[3] reports the age incidence of sarcoma of the vulva as being between 12 and 74 years.

Lannois[4] reported a case of fibrosarcoma of the vulva in a 5-year-old child. Peyrache,[5] in 1905, reported a case of myxosarcoma in a child 8 months old. The tumor had appeared for the first time when the child was 4½ months old.

A case report published by Kuster[6] was that of a 6-year-old child with a round-cell sarcoma of the left labium majus. Ahlfeld's case[7] was that of a girl 3½ years old, who had a sarcoma of the clitoris extending down to the level of the posterior fourchette with metastases filling the pelvis.

CASE REPORT

The case reported in this paper was first seen in the Washington University Pediatrics Clinic in St. Louis, on July 26, 1938. Two months before, when the child was 7 months old, the mother had noticed a swelling in the *right* labium majus of the patient. At first it appeared to be only an area of induration. However, it became progressively larger and, at the time of admission to the hospital, was still increasing in size. During the month previous, hot compresses had been applied to the area since it was thought to be an abscess. During this month the child had been vomiting solid food repeatedly and, although she was taking her formula well, had lost two pounds during the latter two weeks. Throughout this same two-week period the patient had had a cough, nasal discharge, and a low-grade fever. The child was admitted to the St. Louis Children's Hospital the same day.

Physical examination revealed the following pertinent positive findings: The temperature was 37.6° C. The right tympanic membrane was reddened and was bulging posteriorly, with a loss of the light reflex and an absence of the landmarks. The left tympanic membrane showed the same changes, except that there was no bulging of the membrane. There was a profuse mucoid nasal discharge. The liver edge was palpable one fingerbreadth below the costal margin. From the inferior half of the *right* labium majus and extending to the anal orifice there was a hard, slightly elastic mass, about the size of a large walnut. It was not attached to the overlying skin, and, although it was not entirely free at its base, it did not seem to be attached to the underlying bone. The skin over the mass was reddened, but there was no fluctuation or tenderness.

On Aug. 1, 1938, the tumor was excised with a scalpel, using local anesthesia. Histopathologic examination showed the tumor to be a fibrosarcoma.

From the gynecologic service of Dr. Fred J. Taussig, The Barnard Free Skin and Cancer Hospital, St. Louis.

Six weeks later the child was brought back to the clinic. A recurrent mass was noted in the tissues beneath the scar. One roentgen-ray treatment was given over the tumor, consisting of 450 r. with a 200 kv. machine using the following factors: a 50 cm. port, at a target-skin distance of 50 cm.; filter consisting of 0.5 mm. copper and 1 mm. aluminum at 15 Ma.

The patient returned one month later, and no change was noted in the tumor. However, a lump had appeared in the *right* groin which was increasing in size. When the patient was seen again six weeks later, the tumor had increased in size; the mother stated that it had increased quite rapidly during the previous week.

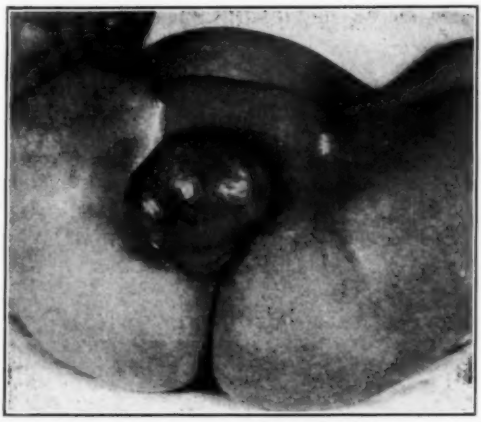

Fig. 1.—Photograph of child in lithotomy position, showing the recurrent mass in the right labium majus.

Fig. 2.—Photograph of child lying supine, showing the fullness in the right groin as well as the recurrent mass.

On Dec. 5, 1938, the child was brought to the gynecologic clinic of the Barnard Free Skin and Cancer Hospital. Examination showed a mass in the right labium majus (Fig. 1) the size of a lemon and extending down to the anal orifice. The mass was freely movable over the underlying tissues, and its consistency was the

same as has been described above. The skin surface was smooth and unbroken, except for a scar at the lower pole from the previous excision. The rest of the genitals were uninvolved, and rectal examination did not yield any additional information. Examination of the abdomen was negative except for the inguinal regions. In the *right* inguinal region there was a mass (seen as a fullness in Fig. 2) 2 cm. by 4 cm., firm, and quite immobile. In the left inguinal region there were several lymph nodes, discrete, freely movable, and apparently of normal consistency.

Roentgenograms were taken of the chest and of the long bones, and when these were reported as showing no evidence of metastases, the child was admitted to the hospital. On Dec. 14, 1938, under drop ether anesthesia, an inguinal lymph node dissection and a radical vulvectomy on the right side were done with the scalpel. Nothing further was done at this time in order not to endanger the child's recovery from the operation. The tissues as shown in Fig. 3 are arranged in their relationships to each other as they were before removal. The large mass is the right vulva and tumor, including the superficial tissues of the right inguinal region just superior

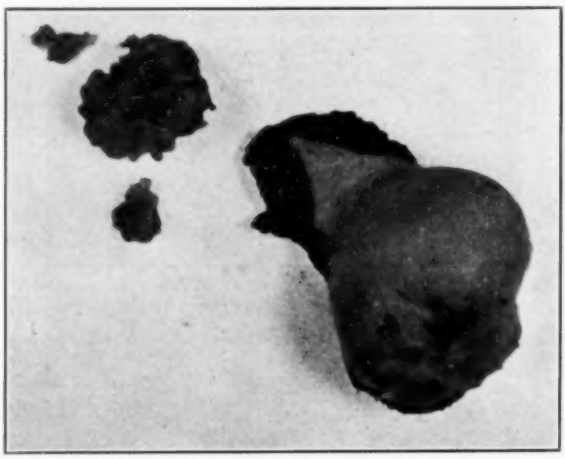

Fig. 3.—Tissues removed by the right inguinal lymphadenectomy and right vulvectomy.

to it. The other tissues are those removed from the inguinal region. The middle one of these represents the mass palpable and visible in the right groin referred to above. The superficial inguinal lymph node, shown in the upper left-hand corner, was removed from the region just medial to the anterior superior iliac spine. The subinguinal lymph node, as seen in Fig. 3 below the middle mass, was removed from the region where the saphenous vein drains into the femoral vein. The postoperative course was uncomplicated, except for an oral infection with *Monilia albicans*, which responded promptly to treatment. The patient developed a nonpitting edema of the right lower extremity, which persisted throughout her illness.

When the child was brought back for observation in February she had gained two pounds in weight, and her general appearance was excellent.

On March 21, 1939, the child was brought back to the clinic, and at this time a mass, 2 cm. by 1½ cm. by 1½ cm., freely movable, and having the same characteristics as the original tumor, was present in the *left* labium majus. The lymph nodes in the left inguinal region were increased slightly in size, and there was a larger number palpable than previously, although their characteristics had not changed. Roentgenograms were again taken of the lungs and long bones, and,

when they were reported as showing no evidence of metastases, the child was readmitted to the hospital. At this time, nine days after the tumor was first seen, it had increased to half again its original size, and the skin over it was ulcerated at two points. Under drop ether anesthesia the *left* vulva was removed and a left inguinal lymph node dissection was done as before. The postoperative course was

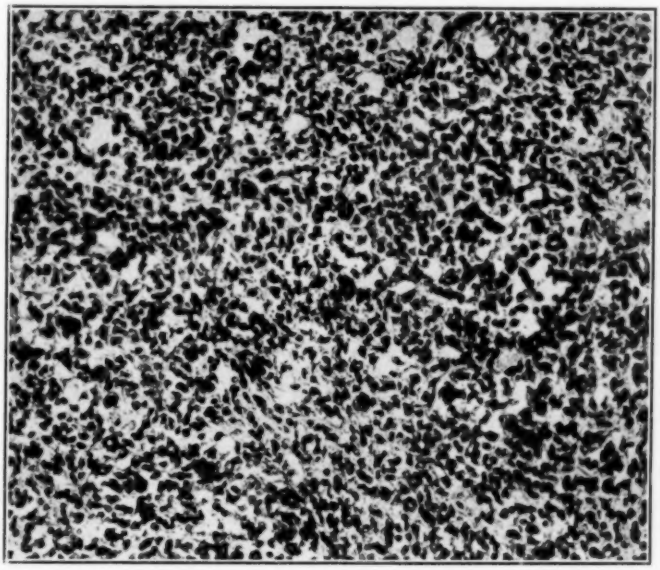

Fig. 4.—Microscopic picture of tissue from the right vulvectomy. (×140.)

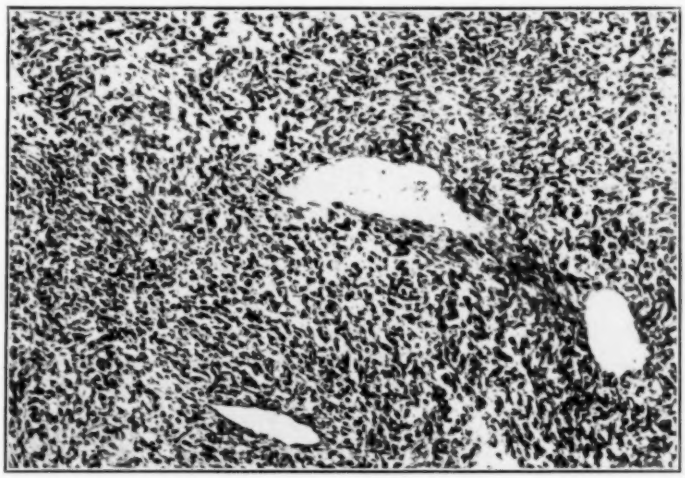

Fig. 5.—Microscopic picture of the metastatic mass in the right inguinal region. This shows a more undifferentiated growth than Fig. 4. (×140.)

afebrile and uncomplicated. The length of hospital stay for each operation was approximately three weeks.

The patient was brought to the clinic for observation on May 3, 1939. She had gained weight again (about 7 pounds). However, at this visit it was noted that there was a small area of induration inferior to the right wound, 1½ cm. by 2½ cm. in diameter. It was decided not to do anything and to watch this.

Seven weeks later the child had lost considerable weight and developed diarrhea. At this time the abdomen was found to be quite distended, and the induration below the right wound was more prominent. Moreover, this induration had extended to the subcutaneous tissues of the lower abdominal wall in the right lower quadrant to the midline and to a point superiorly midway between the symphysis pubis and the umbilicus. On rectal examination a firm, immovable mass 3 cm. by 2 cm. was found to be present in the pararectal tissues on the left side, just anterior to the level of the rectum.

Thereafter, the child's condition became progressively worse until she died on Aug. 8, 1939. No post-mortem examination was done.

Histopathology.—Microscopic examination of the tumor removed from the right labium majus showed the spindle-shaped cells of a fibrosarcoma (Fig. 4). In certain portions the cells are highly undifferentiated and show a strong tendency to anaplasia.

A section taken from the mass in the right inguinal region (Fig. 5) revealed the same type of cells, except that the majority of them were very anaplastic.

The two small lymph nodes removed from the right inguinal region in the dissection showed no evidence of any metastases.

The mass in the left labium proved to be the same type of tumor, but the lymph nodes removed from the left inguinal region showed no evidence of any metastases.

DISCUSSION

In the case presented in this paper, the patient was subjected to careful roentgenologic examination for distant metastases both times before being subjected to surgery. Only when no evidence of metastases was found were the operations performed.

One of the remarkable observations in this case was the general appearance of health and well-being of the child. This was one of the most important factors in prompting the surgical treatment of this case.

As may be noted by perusal of the history, the original tumor, as well as the recurrences, seemed to grow slowly, and then suddenly to gain momentum and grow rapidly. At the time that decisions for surgical treatment were made, the lesions were present locally or had recurred locally, with metastases localized to regional lymph nodes on one occasion.

Complete removal of the lymph nodes at each operation was not done. Only the inguinofemoral group of nodes was removed. The obturator and external iliac lymph nodes were not removed. It was not deemed feasible to prolong the operation to this extent.

The poor response of fibrosarcomas to radiation is a well-known fact. Whether a combination of surgery and prophylactic radiation would have offered a more hopeful prognosis is a moot question.

This is the type of case which should be considered from the viewpoint of "cancer optimism." There are probably quite a few cases of malignant neoplasm, in early stages, which are "condemned to death" unfairly because the eventual outcome seems hopeless. If the child had been brought to a gynecologist for the first time in its terminal state and had been subjected to surgery, then that gynecologist could be justifiably accused of lack of sober judgment. The fact that the lymph nodes in the left inguinal region showed no evidence of metastases and that the last culminating metastases were in the right inguinal region seems to convey a particularly poignant significance. Would this child have had a better probability of longer survival, or even cure, if radical surgery had been resorted to at the very first diagnosis of the tumor? We cannot help but feel there may have been a different outcome if this had been done.

SUMMARY

A case of fibrosarcoma of the vulva in a 7-month-old infant is presented. Comparatively radical surgery was resorted to in this case. Only four other cases have been reported in young children.

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AN ADAPTER FOR URINE SPECIMEN TUBES

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IN THIS brief communication the substitution of a sterilized rubber adapter for adhesive tape on the mouths of test tubes used for the collection of urine specimens from infants and small children is offered. The use of the rubber adapter provides a smooth protective surface which is not always attained with adhesive tape. While the application of adhesive tape to the collecting tube in our experience is time-consuming, the rubber adapter is easily adjusted to the tube in a short time. In addition, the test tube can be sterilized with the adapter attached. Lastly, the firmness of the grip of the adapter on the tube makes it safe for use on patients without risk of removal during continuous collections of urine. The use of the cloth hammock for suspension of the test tubes on patients is still desirable.

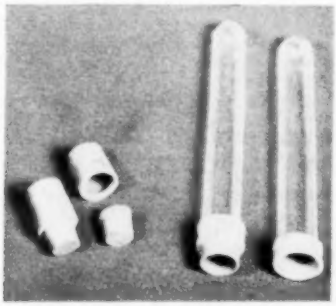

Fig. 1.—Various stages in the preparation of an adapter for a urine specimen tube.

This adapter is made by removing the plunger of a Noair rubber stopper* with a cork borer. This removal leaves an opening through which the mouth of a test tube is inserted. Approximately 3/8 inch of the rubber collar is permitted to extend above the rim of the test tube, and then this projecting portion of the collar is tucked back into the mouth of the tube (Fig. 1) so that a smooth, close-fitting, rubber inner rim can be obtained. The use of No. 5 Noair rubber stoppers with test tubes having an outside diameter of 3/4 inch and a flare at the mouth proved to be convenient. It was found necessary to use No. 4 Noair stoppers on test tubes having a diameter slightly less than 3/4 inch.

From the Renziehausen Memorial Ward, Children's Hospital of Pittsburgh.
*The Noair rubber stopper is a product of the United States Rubber Co.

PSYCHOLOGIC CARE OF THE PRESCHOOL CHILD

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PART III

H. Parental attitudes
- Affection
  - Overaffection
- Overprotection
- Overindulgence
- Overanxiety
- Underaffection
  - Indifference
  - Rejection
  - Parent-child antagonism
- Overauthority
- Identification
- Perfectionism
- Parental incompatibility

I. Sibling rivalry

H. PARENTAL ATTITUDES

THE most important factor influencing the development of personality in early childhood is the attitude of the parents. Sayles[24] says: "Whereas all children start out in life with substantially the same emotional needs, this is far from true regarding the parents. Their attitudes toward the first child will be colored by the extent to which their own childhood needs were met and by their later emotional history as adolescents and adults; and their behavior toward subsequent children will be further modified by their experiences with previous children. These demands for emotional satisfaction may be compatible with a proper development of the child's needs or they may more or less seriously interfere with the child's normal progress." In any consideration of the personality development of the child, therefore, a survey of the parental personalities is of the first importance.

AFFECTION

The normal attitude of the parent toward the child is one of affection, and it is fair to state that this is essential for the proper personality development of the child. A real sense of security develops only when the child feels that he is loved and understood. Under unusual circum-

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stances, however, the normal parent-child relationships may be modified, in the direction of excessive or deficient affection, with more or less serious consequences to the child. The attitude of the parents toward the child may be influenced by their personalities and upbringing, by external conditions such as the economic situation, by prevailing views regarding the proper methods for rearing children and by the interparental relationships.

The patterns of mother-child relationship are frequently well established in infancy and are often dependent upon factors operating before the birth of the child. The effect on the child is usually not observed before the end of the first year and becomes more and more marked during the preschool period.

OVERAFFECTION

Overaffection, an exaggeration of the normal affectionate attitude of the parent toward the child, is not infrequent and may be seen in any situation where the desire for a child is increased. It is often observed where there is an only child, particularly if the child has been born after the parents have been married for a long time or where there have been several miscarriages or death of a previous child. It is also likely to occur if the pregnancy or labor has been difficult or if the child has had a serious illness. Overaffection is sometimes seen in large families where the age interval between the last child and the previous children is great; and in this situation the youngest child may get excessive affection not only from the mother but from the siblings as well. Adopted children are frequently subjected to this attitude because they have been desired for a long time. Boys are more often affected than girls.

The emotional history of the mother plays an important part in the etiology of overaffection.[25] The mother, coming from a home where there is too little affection and too great responsibility, often marries to free herself from her unhappy environment and consequently marriage is likely to be unsuccessful. Unsatisfactory sex life, parental incompatibility, and lack of social interests intensify the mother-child relationship. The excessive affection is most often maternal but may be exhibited by the father or by both parents.

Overaffection is frequently accompanied by overanxiety and by overindulgent, overprotective, and oversolicitous behavior, and the effect on the child is dependent on the manner and the degree to which these are present. Children who are overindulged, overpraised, and overpetted by the adults surrounding them are poorly prepared to share their place in the household when a new sibling arrives or to mingle on equal terms with their peers in the playground and in the school room. Furthermore they often fail to utilize their developing potentialities, preferring to remain immature since those who have been responsible for their upbringing have not made the growing-up process attractive enough.

OVERPROTECTION

Overaffectionate parents usually show overprotective behavior toward their children although overprotection is also seen where there is parental rejection. By prolonging infantile care through excessive control, the mother prevents the development of independent behavior. She spends most of her time with the child, not permitting him to play with other children, and she continues to feed and dress him long after he is ready to do these things for himself. This retardation, however, does not refer to the establishment of bladder and bowel control, which is ordinarily acquired at the usual time or even earlier. The behavior of the overprotecting parent toward the child is characterized by inconsistencies, the parent being overauthoritative about certain activities and overindulgent about others. The child is freely indulged as far as toys and play are concerned, but a firm stand is maintained where the child's personal safety or separation from the mother is involved.

In families where there is overprotection, the fathers appear to exert little control. They are likely to be submissive to their wives and are often indifferent to the situation. In rare instances there is overprotection of the child by the father. There may also be rivalry between mother and grandmother to protect and care for the child.

The outstanding effect of overprotection on the child is immature conduct which may manifest itself by aggression, submission, or, rarely, indifference. Aggressive behavior, which is most common, results from lack of maternal control and overindulgent overprotection. The child attempts to control every situation, refusing to yield to any authority and indulging in generally undisciplined behavior such as impudence, temper tantrums, bullying, and cruelty to younger children. Irresponsible behavior and refusal to do one's share are prominent symptoms. Where the mother has a dominating personality, there is submissive and effeminate behavior, the child being irresponsible, dependent, and immature. He is docile and runs to his mother for protection. He is likely to persist in infantile habits, insisting on being dressed, washed, and fed. Eating difficulties are often present.

A common characteristic of overprotected children is their inability to make friends. The most frequent objection to playing with these children is either that they want to control and lead the games, or that they are afraid of rough sports and depend too much on the help of their mothers. In either case they refuse to play with other children on an equal basis. Often they become accustomed to adult society and do not know how to play with children. Difficulty in making friends further reinforces the maternal overprotection by excluding the child from the companionship of children of his own age.

Prophylaxis.—The parental overprotective attitude can be modified, if not entirely prevented, if the physician is alert to those situations which give rise to overprotection. Thus, when a long-desired child is born

under any of the circumstances enumerated above, the parents should be warned concerning the ill effects of overprotection on the child before parental attitudes have become fixed. Similarly when a child suffers a severe illness, opportunity should be taken during convalescence to caution the parents about their attitude. Where the overprotective attitude is closely bound up with the personality of the mother, the situation is more difficult to handle, but even here much can be done by a clear explanation of the effect of overprotection on the child. The mother should be urged to develop interests outside the home. Specific directions should be given to aid the child in acquiring various techniques of self-dependence, such as washing, dressing, feeding, and taking responsibility for play away from home. At the same time the value of discipline in helping the child to fit into his group should be explained.

Treatment.—Before the treatment of overprotection is undertaken, it is essential that an accurate differentiation be made between the overprotection associated with overaffection and that seen with rejection. This is not always easy and often depends upon careful observation of the situation over a period of time.

In a young child the immature behavior resulting from overprotection may be treated with a fair degree of success. No approach will be effective without an explanation to the parents of the influence of their attitude on the personality of the child. The child should be encouraged at first to do those things alone which he is able and willing to do. The pleasure which he obtains through achievement will often encourage him in further acts of self-dependence and will also demonstrate to the mother that the child has potentialities of which she was not aware. The child should be gradually accustomed to playing with other children. A beginning should be made with one or two children, and the group slowly enlarged as the child makes adjustments. Where the overprotected child is receiving attention continually with no differentiation between good and bad behavior, the mother should be instructed to differentiate between requests which are reasonable and those which are made solely to get attention. Approbation should be given for good behavior, and care should be taken that the child is not rewarded in order to pacify him.

The mother should be encouraged in interests outside the home. This will serve to lessen the intensity of the bond between her and the child and at the same time may compensate to some extent for those defects in her childhood and married life which may have led to her overprotecting attitude. Discussion with other mothers of their problems with their children will often bring a better understanding of the influence of parent on child.

OVERINDULGENCE

Overaffectionate parents are frequently overindulging. The child receives everything he desires, so far as it is financially possible, and is

permitted to do whatever he pleases. Grandparents are frequently overindulging. The grandmother often feels that, inasmuch as she sees the child so seldom, she has a right to enjoy him as she wishes. Sometimes the child is bribed in this way to pay more attention to the grandmother than to the mother.

Parents who indulge their children are most often those who have had an unsatisfactory childhood, associated with financial worries or hardships. They find their children attractive and enjoy pleasing them. Fathers are more apt to be indulgent than mothers, perhaps because they are not so acutely conscious of the unpleasant results of overindulgence. Although overindulgence is most commonly associated with overaffection, it is found also where rejection is accompanied by a feeling of guilt on the part of the parent. Here the parent indulges the child to ease his conscience. With rejecting parents the indulgence is often sporadic, alternating with periods of overauthority.

Overindulgence impedes the child's emotional development, keeping him in the infantile dependent state where a fit of crying or a temper tantrum is sufficient to summon the parent to satisfy all demands. The overindulged child is the demanding child. Accustomed to get what he asks for, he insists upon prompt response and resorts to tears and outbursts of anger if he does not obtain results quickly enough. His demands are often unreasonable since all reasonable requests have already been satisfied. He expects to be pampered and gets along poorly with other children who will not cater to him. He requires entertainment and is usually quite incapable of amusing himself. He is often bored, and the adults about him are kept busy devising diversions for him. His behavior cannot be relied upon when visiting as he is uncooperative and demands attention continually. The parents concede to the child's demands at first, but as he grows older and more demanding they frequently become annoyed and irritated at his behavior. They are unable to cope with the situation which their attitude has created.

The parents should plan and carry through a consistent method of treatment. They should impress on the child the advantage of more reasonable behavior by consistently refusing to concede to infantile demands and by giving praise and satisfaction for more mature behavior. If the child is old enough, the parent should explain to him the reason for this change in attitude and should warn him that demanding behavior will no longer bring pleasant results but will, instead, be met with deprivations. At the same time the child should be assured that he is still loved and is really being benefited by this new method.

PARENTAL OVERANXIETY

Parental overanxiety, though more frequent in mothers, is not uncommon in fathers. It is often seen where there has been a serious illness or death among the children or other members of the family or among

the children of friends. It is more often observed in families where there is an only child upon whom all the hopes and desires of the parents are centered. Where there is marital incompatibility, the maternal interest may be entirely centered on the child and this is intensified when the mother lacks interests outside the home.

Overanxiety is usually associated with overaffection and overprotection, but it may occur alone. There may also be overindulgence. Overanxiety is seen at times in the rejecting parent.

Parental overanxiety manifests itself by oversolicitous conduct. The child's activities are limited because of the parental fear of disease and accident. He is not permitted to play freely with other children, and companionship is limited because of the fear of contagious illness. He is not allowed to participate in sports, nor may he go about unaccompanied by an adult because of the danger from traffic, strange people, etc. Minor illnesses are exaggerated, and the child is kept from school and in bed for an unnecessarily long time.

The child responds to the parental overanxiety by timidity, fearfulness, shyness, and cowardice. Since he has never been taught how to meet a situation alone, he becomes dependent upon his parent for direction. He is apt to become apprehensive and overanxious about his health.

Mild degrees of parental overanxiety are very frequent at the present time because of the prevalence of small families and of the hazards of life in large cities. Except where exaggerated, both children and parents make a good adjustment to this situation. A discussion with the parents of the undesirability of their attitude and its effect in limiting the child's developing self-dependence and initiative will materially assist in clarifying matters if the parents are ordinarily sensible.

UNDERAFFECTION

By parental underaffection or rejection[26] is meant dislike of the child by the parent. The degree of dislike may vary from mild indifference to intense aversion. It may be present at the time of birth of the child or may develop later in childhood, and its appearance can often be predicted by the attitude of the parents during pregnancy. It is by no means uncommon.

Parental indifference, or lack of parental interest in the child, results usually from the lack of close association between parent and child. The activities of the mother may be mainly outside the home for economic or social reasons, and she may have little time for the child and little interest in him. In a large family, or where the child is assigned to a nurse, the mother may not have the opportunity to become acquainted with her child. The father may make demands upon the mother's time, expecting her to do things for him or with him which keep her away from the home. It is not unusual for the father to lack association with

the child since his main interests are usually outside the home. The child may receive all material comforts but lack affection. The effects of parental indifference are best seen in the orphaned child. Indifference is frequently encountered in families where there is a stepmother or stepfather, the child's own parent often being unwilling to spend much time with the child whom the stepparent may not accept.

The child often seems to accept the situation and conforms as is expected of him. He is, however, usually insecure and feels himself inferior either in not having the opportunity to be loved if he is an orphan, or in not being worthy of affection if he has parents. He appears to accept the indifference of his parents, and he may in turn stop loving them and try to find a parent substitute who will love him and whom he may love. As he grows older, he is unappreciative of his home and of what his parents have given him and is often openly resentful toward them.

The inadequacy of affection in orphan homes and the unfortunate effect upon the child have recently been recognized, and boarding homes and foster parents have been substituted in many instances. The parents in these homes usually desire the children and give them a certain amount of affection, attention, and praise. In general the children improve under this treatment.

Treatment.—Parents should be taught to feel responsible for the emotional as well as physical health of the child. Fathers should learn that providing an adequate income is not their only function. Paternal lack of interest sometimes results from the feeling of uselessness developed at the time of birth of the child. This can often be avoided if the father is made to feel that he is wanted and needed and can actually be helpful with the newborn infant. For parents who have business and social interests which keep them away from home during the day a schedule can be arranged so that they may have time with their child when they are at home. This may mean a revision of their routine or of the child's, but it usually is possible. An interest in the child's activities will often pave the way for a better understanding between parent and child.

REJECTION

Rejection is likely to arise under any set of circumstances where the child is unwanted. It is often seen where marriage is precipitated by a premarital pregnancy, and the child was not desired. Rejection by a mother who has shown disgust of sexual relation or fear of pregnancy is occasionally observed. It may also occur where the birth of the child leads to economic difficulty. The second child in a family is sometimes rejected because the added financial burden which his advent imposes may deprive the first child of advantages which the parents had planned for him. Rejection may occur solely on the basis that the child is not of the desired sex. This is usually seen where all or most of the previous

children are of the same sex. In some cases, where disappointment regarding the sex of a child is strong, the parents may give the child a name more usual for the other sex and may even encourage the child in attributes common to the other sex. A child may be rejected because he is sickly, ugly or cries a great deal and keeps the parents awake at night. This is more likely to be paternal than maternal. Some mothers reject a child because he interferes with their employment outside the home.

Rejection may have its origin in the personalities of the parents, in the interparental relationships, in parental jealousy of the child, or in failure of a child to live up to parental expectations.

Of the parental personality attributes which lead to rejection of the child one of the most common is parental immaturity, i.e., the parents have not matured to the state where they are willing to make the sacrifices which parenthood necessarily implies. According to Foley,[27] this self-centered attitude in the parents is fostered by an upbringing in which the individual had plenty of affection but had little responsibility. This is not uncommon in young mothers who were popular with men before marriage and who look upon the child as a symbol that they are growing old. Parenthood requires a maturity of viewpoint and a self-sacrificing attitude which many young mothers are slow to acquire. This attitude is much more common toward the firstborn than later born children and is often not permanent. In exaggerated form this parental personality pattern is sometimes referred to as narcism, by which is meant "fixation on oneself or gratification through the love of oneself."

Where there is parental incompatibility, the child is frequently rejected because he is considered an impediment to a possible separation of the parents. In such instances, also, the child may be rejected because he reminds the parent of the disliked mate. Where insanity, drunkenness, or other undesirable tendencies exist in the family of one of the parents, the parents may feel it undesirable to have a child because of the possibility of transmitting these characteristics. In such instances the child is usually resented by the parent whose family is not so afflicted. There may also be a guilty feeling for marrying into such a family. Rejection may occur where there is parent-child jealousy. When extreme, this leads to parent-child antagonism. When a child is not able to accomplish what is expected of him at home or in school, he may misunderstand the parental disappointment and interpret it as dislike. Such a situation, if brought to the attention of the parent, may be readily corrected. Occasionally real rejection may develop out of the disappointment which the parent feels.

Among a considerable number of parents the normally affectionate attitude toward the child is tempered by a feeling that affection is undesirable for the child, that it has a softening influence, and that it is old-fashioned. This attitude is doubtless used by some parents to rationalize an emotional indifference to the child, but it may represent a

sincere attempt on the part of the parents to give the child a proper upbringing. Where the mother is employed away from home and so has little time to spend with the child, the child may feel neglected and unwanted, even though the parent is not really indifferent. This same feeling may occur when the parent is unable or unwilling to show affection which actually exists.

Rejection may be overt, that is, obvious and recognized by the parent, or it may be obscured by conscious or subconscious efforts at concealment. Mothers who are effusive in their attentions to the child may be actually rejectors. Paternal rejection is usually overt. The overprotection not infrequently associated with rejection of the concealed type has its origin in a sense of duty or feeling of guilt on the part of the parent.

The behavior of the rejecting parent toward the child is characterized by lack of appreciation amounting to continual criticism. The parent is unable to see the good points in the child and minimizes his successes. On the other hand, the child's undesirable traits are overemphasized and minor deviations in behavior magnified. The rejecting parent is impatient, overcorrective, and often a rigid disciplinarian. The home atmosphere is one of nagging and discontent. When rejection is combined with a parental sense of duty, with or without a feeling of guilt, the child may be given everything possible in a material way in an attempt to compensate for the lack of affection. To ease his conscience the parent may go even further, making personal sacrifices for the child and even overprotecting him. It is this type of behavior on the part of the rejecting parent which makes the differential diagnosis from overaffection difficult.

The outstanding personality defect in the rejected child, whether overt or concealed, is lack of a sense of security, which requires an affectionate home atmosphere for its proper development. Behavior characteristic of the insecure child is usually evident in all rejected children.

When parental rejection is overt, there is usually aggressiveness and a desire for revenge, mixed with hypersensitiveness and unhappiness. The child is selfish, resentful, vengeful, disobedient and quarrelsome, often unpopular with other children, restless, and hyperactive. Temper tantrums, lying, stealing, and running away are not uncommon. The child is usually anxious for attention and will seek the most annoying means of getting it. The aggressive behavior is most evident when the rejecting parent is the father.

Where the rejection is concealed and associated with overprotection so that the child is not fully aware of his rejection, behavior is more apt to be submissive. The child is shy, secretive, and fearful. He cries easily, is unable to concentrate, and often shows poor achievement at school, irrespective of his intelligence. He is apt to be unpopular with his playmates.

In all types of rejection the child's need for affection leads to excessive demand for attention and applause.

Prophylaxis.—The most important factor in preventing parental rejection is an early appreciation by the physician of the circumstances under which it may arise. It is only by early recognition of the rejecting attitude, before parent-child relationships become firmly established, that the best results can be obtained.

The rejecting attitude of the parent may be suspected during pregnancy. At this time a common-sense discussion of the circumstances which the parent seems to resent may assist materially in clarifying a situation potentially harmful to the child. A fixation on the sex of the child should be discouraged. When parents feel that the birth of a second child may deprive the first child of material benefits they have planned for him, the advantages of companionship of the two children should be emphasized. If the advent of the child is thought of as an impediment to a career outside the home, a more thorough understanding by the mother of her relation to society may show her that ultimately the career of woman is that of a mother and that her activities outside the home are probably temporary.

During pregnancy the mother should be instructed in her attitude toward her husband so that he will not feel useless, neglected and resentful toward the child when he arrives. Wherever possible, the potentially rejecting mother should be induced to nurse her child, as the likelihood of rejection arising in a nursing mother is considerably less than in the case of an artificially fed infant.

Treatment.—With intelligent parents an explanation of their rejecting attitude, which is frequently unconscious, may help greatly, particularly if instituted early in the child's life before parental attitudes have become fixed.

Before treatment is attempted, an estimate of the mechanism leading to rejection in the particular case is essential, and the situation should be discussed with the parents accordingly. If parents can be made to realize that they are demanding more of the child at home and at school than he is capable of giving, and that the child is not responsible for his inadequacies, a difficult situation can often be resolved. Furthermore, by release from the psychic discomfort resulting from parental criticism, an improvement in the child's achievement is often effected.

When the mother uses the infant as a means of getting attention and sympathy from the father, this should be discouraged.

Although it may be difficult for the parents to give affection to the child, they should be urged to encourage him by applauding his successes and minimizing his failures. Invidious comparisons with siblings, nagging, and overcritical attitudes should be avoided.

Parent-Child Antagonism.[28]—An extreme form of rejection is observed in the condition often referred to as parent-child antagonism.

Parental antagonism is usually directed toward a child of the same sex as the parent and most often by the father toward the son. The usual basis for this feeling is parental jealousy of the child. The father may consciously or subconsciously resent the normal attachment of the mother for the child and the time and care which she devotes to him. The son, sensing the paternal antipathy, avoids the father and clings to the mother, thereby sharpening the antagonism. Some fathers are actually cruel and continually exaggerate minor transgressions of the child in order to justify their own feeling of hostility. The child, in turn, continues his transgressions in order to annoy the antagonistic parent and in this way delinquent conduct may arise.

The father may not be aware of his hostility toward the child and may even actively resent any suggestion that this is the case. He may insist on a standard of performance which the child is unable to achieve and then use the child's failure as proof of the validity of his own attitude.

Some fathers see their sons as competitors or rivals and treat them with great hostility and cruelty. This has been interpreted as a carry-over of the sibling rivalry of the father's youth. A child may be blamed for maternal illness associated with his birth or for any later maternal illness, or for premature aging of the mother. He develops a sense of guilt, often accepting the blame placed upon him, and becomes fearful, uncertain and convinced of his own worthlessness. This is a most unhappy group of children and comprises many of the runaways and truants.

A few children who are unhappy at home because of the hostile atmosphere do unusually well at school and are well liked by their school friends, possibly because of the friendlier environment at school and the desire to succeed where a fair chance is given.

PARENTAL OVERAUTHORITY

There are parents who are unable to accept the child as he is but require that he react in accordance with their ideas. They expend great energy and exert excessive authority to train him. Some parents, with a strong feeling of inferiority, may feel thwarted if the child fails to respond in the desired way, and they therefore assume a domineering attitude in order to appease their offended sensibilities. In some instances there is a sincere belief that this is the best way to prepare the child for the future. The overauthoritative parent is usually unduly critical and nagging and may be actually rejecting.

The characteristic response of the young child to overauthority is submission accompanied by resentment and evasion. Fearful of openly refusing to follow commands, the child resorts to dawdling over eating, dressing, washing, etc., and is often characterized as a slow child. He rarely disobeys directly but seeks methods of evasion, such, for example, as concealing food which he was commanded to eat, or saying that he

has not eaten *a* candy when he has eaten *two*. The child obeys the letter of the command but not the intent. This dawdling, evasive behavior is very characteristic, and, when encountered, should lead the physician to suspect an overauthoritative parent.

Many parents fail to appreciate that they are too domineering, or that they are trying to force the child into a preconceived pattern of behavior. They do not realize that their insistence on strict compliance leads to evasive behavior which may be a forerunner of deception and which in itself is much more serious than nonconformity.

In dealing with the overauthoritative parent, emphasis should be placed upon the importance for the child of developing his own potentialities. The parent should be urged to try to see the child's point of view and to manage situations with kindness and understanding rather than in accordance with a preconceived idea of what the child ought to be.

PARENTAL IDENTIFICATION

Parental identification refers to the attitude of the parent who relives his life in the child and who wishes for the child those things which he has wanted and not obtained. These may be specific desires for education, financial security, travel; or more vague and perhaps more compelling desires for affection, independence, or success.

When the identification is between mother and child, the mother is likely to demand excessive affection from the child to make up for her early deprivation. The mother may also impose her interest in sports, music, or society on the child. Where there is paternal identification, the father is usually eager to compensate for his own lack of education or business opportunity. He is often overambitious for the child, setting high standards and urging the child in the direction of his own interests.

In most instances the child is very much wanted and is considered well-nigh perfect during infancy. As he grows older and fails to show interest or to succeed in the fields where his parents expect his success, disappointment results. Even the small child may sense the parental disapproval and as a result he usually becomes quiet, shy, retiring, and insecure. He cries easily and often will not attempt the simplest tasks because of his fear of failure, thereby leading the parents to believe that his inadequate behavior is due to obstinacy.

Parents with this attitude are sincerely anxious to help the child and can usually be made to understand that the child's desires and interests may run counter to theirs, thereby causing his failure. When they grasp the situation they will usually help the child to follow his own desires. As soon as parental pressure is relaxed and the child finds sympathy and understanding, he begins to develop into a much more satisfactory individual.

PERFECTIONISM

Some parents are unduly ambitious for their children and make demands on them which are beyond their capacity. Anything less than perfect behavior is unacceptable, and little credit is given for improvement unless the achievement is fully successful. Much of the child's time is spent in extracurricular instruction as the parent expects success not only in the usual daily routine but in music, dancing, sports, and reciting. Some of these parents demand perfection to bolster their own ego and to compensate for a feeling of inferiority. Others feel that the child's success in life is dependent on a good foundation and falsely believe that they are giving the child this opportunity for success. The heavy schedule which is imposed on the child is fatiguing, and as a result he is likely to be overanxious, unstable, and hyperactive. He sleeps badly, has poor appetite, and indulges in nail-biting, picking at clothes, and generally restless behavior.

Children cannot thrive under completely routinized living conditions. Free hours, free play, and free direction of energies are essential. Encouragement and deserved praise yield much better results than overdirection and criticism.

Overresponsibility.—Some parents expect their children to accept more responsibility than they are psychologically ready for. The technical ability to perform a task does not necessarily imply that the child is ready to take the responsibility for doing this by himself. A sense of responsibility involves the ability to put aside all distractions and temptations and to realize the advantage of satisfactory accomplishment. On the whole parents tend to demand too much responsibility when children are small and too little when they are older.

Responsibility for punctuality should not be expected of a child until he is 7 or 8 years old. Neatness and cleanliness, especially in a boy, develop only as he nears adolescence. A small child cannot be expected to have an understanding of honor or to remember admonitions over a long period. Instead he should be safeguarded against temptations in proportion to his ability to withstand them. An older child may learn to forego pleasures for something more important in the future or for parental approval or personal satisfaction, but this should not be expected of a younger child.

Overresponsibility is frequently associated with overauthority, the parent demanding success from the child in acts for which he is assumed to be responsible. It is also seen where there is parental rejection, but conscientious, affectionate parents who have erroneous notions about child rearing may behave in this manner.

When the child is given greater responsibility than he is ready for, he may appear more mature than usual for his age, seeming quiet, serious, and industrious. Actually there is often a reversion to the infantile

with bed-wetting, restless sleep, and childish play. Sometimes the child refuses to accept the responsibility and pretends he is unable to perform even simple tasks, thus evidencing his immature reaction.

Although the child should be helped in the growing-up process there should be no attempt to hurry him. Training in various skills and responsibilities must wait until the child is developmentally ready to profit by such training. Only by allowing him to assume control at the proper time can he develop to the fullest extent.

PARENTAL INCOMPATIBILITY

The effect of parental incompatibility on the personality development of the child depends on (1) the child's awareness of the situation which, in turn, will be dependent on the child's age, mental alertness, and the parental efforts at concealment and (2) the personalities of the parents.

Most young children look upon their parents as perfect. The bickerings and recriminations to which the child is exposed shake his convictions and confuse him. He is torn between parental loyalties, siding first with one parent, then with the other. He is ashamed and tries to conceal the parental incompatibility from his friends. One parent may make a confidant of the child, currying favor with him, and implanting antagonism toward the other parent. Sometimes a child is used by one parent to spite the other, and the child may be encouraged in conduct of which the other parent disapproves. Again the child may become the sole outlet for the maternal affection and thus maternal overaffection, overanxiety, and overprotection may further influence personality development.

Incompatible parents are frequently inconsistent in their attitudes toward the upbringing of the child. They fail to consult together, and therefore their attitudes toward privileges and prohibitions are frequently conflicting. Parental incompatibility is likely to occur where there are personality defects in one or both parents, and therefore in analyzing the influence of parental incompatibility the parents must be considered individually as well as together.

The effect of parental incompatibility on the child is primarily a feeling of insecurity. The child needs to feel that he belongs to both parents. If one parent is pitted against the other or if both use the child as an instrument for hurting one another, his security is threatened. The child also suffers conflicts of loyalty, mixtures of love, hatred, and hostility. He may turn completely to one parent and rebuff the other, or may try to be loyal to both. Often he regresses to infantile acts, such as bed-wetting, thumb-sucking, whining, fearfulness. A sense of guilt may be combined with uncertainty and embarrassment, the child feeling that he is in some way responsible for the difficulties between his parents since many of the quarrels which take place in his presence

concern him. Recollection of previous compatibility between the parents while he was small may lead the child to feel that his growing-up is a reason for the friction. The preschool child will only sense this and will probably not feel the responsibility for trying to adjust matters between the parents which older children experience.

Important also is the child's fear that he differs from his group. During the school years and sometimes earlier it is important in the child's mind that he conform and so be accepted by his friends. Being different embarrasses him and he responds with feelings of shame or fear, and an unwillingness to produce his parents, a situation which the group quickly senses.

It is not unusual for the child of incompatible parents to be rejected. His presence during their quarrels may cause the parents to feel guilty and so resent the child. Also he may interfere with their possible separation and so become undesirable. Some parents feel that the child is actually responsible, as many of their disagreements concern him. Occasionally the affection between mother and child causes the father to feel jealousy or resentment not only toward his wife but also toward the child.

Some children, by developing a hardness and self-sufficiency, seek an escape from disappointing parents. Others, more fortunate, find substitutes for their parents among teachers or older children, while a few try to escape into a dream world which excludes the distressing realities.

Separation or divorce of the incompatible parents eliminates friction in the home but often makes the situation more difficult for the child since the parental incompatibility, which he has more or less successfully concealed from his friends, becomes an established fact which he must now accept and explain.

Treatment.—There are a few suggestions which may be helpful in handling the children of incompatible parents. There should be no quarreling in the presence of the child. The parents should be urged to be consistent in the treatment of the child. It is unfair either to confide in the child or to play the child off against the other parent. Furthermore, if the parents must separate, the child should be warned and helped to understand and to accept such a step. He should be shown that disgrace does not necessarily accompany this act.

Occasionally a child may wrongly interpret the attitude of one parent toward the other, and may believe that friction is present when instead there is a real understanding. In such instances the parents' attitude toward the child and the reason for his misunderstanding the situation must be gone into and corrected.

In any case the child's attitude toward the home situation may be modified by careful guidance. He should be assured that he is in no way responsible for the unhappy situation.

I. SIBLING RIVALRY

Sibling rivalry, or jealousy of the child for a brother or sister, is very common.[29] It is seen more frequently in firstborn than in subsequent children since the first child has had no opportunity to learn to share the parental affection and attention with a sibling. It is more likely to persist in small than in large families because the children in large families soon learn to comprehend the division of affection which arises with the advent of each new child. Furthermore, there is less chance of exclusive maternal devotion to any given child and more possibility of compensatory friendship between children and of sympathy and solidarity among the older children.

Sibling rivalry is likely to be most intense when the older child is between 18 months and 3 years old at the time of birth of the younger child, since at this age the child has already become aware of the parental affection, but he does not feel well enough established in the esteem of the parents to be willing to share with a sibling. Furthermore, during this age period, the child is still to a large extent psychologically dependent on the parents. Sibling rivalry is less keen in brother-sister combinations than when the children are of the same sex since there is less apt to be a clash of interests.

The intensity of the rivalry feeling is, in general, proportional to the dependence of the child on the mother, and hence the overprotected child is apt to be jealous of a younger sibling. Sibling rivalry is also observed where there is parental rejection and in such instances it represents another outlet for the child's general psychologic discomfort.

The response of the jealous older child is most frequently hostility toward the newcomer combined with a desire to relive the pleasures and advantages of infancy. Hostile behavior toward the younger child may be overt, manifesting itself by cruelty and an attempt to get rid of the baby; or it may be concealed and displayed in a more subtle manner by persistent demands for attention when the parent is occupied with the baby. At times an attitude of tenderness and protection is mixed with hostility, and the older child may assume a possessive role toward the infant. Infantile responses in the jealous child appear as wetting, soiling, insistence on being fed, held, rocked to sleep, etc.

Favoritism of a nurse for the younger child frequently intensifies sibling rivalry, and this is particularly likely to occur when the nurse is employed after the birth of the second child. Infant nurses are trained in the care of infants and have little if any instruction in the handling of older children. They tend to focus their attention on the baby where their success can be measured by the weighing scale and look upon the older child as a secondary responsibility.

Prophylaxis.—Since sibling rivalry is more likely to occur in overprotected and in rejected children an attempt should be made to en-

courage the child's self-dependence and at the same time make him feel secure in the affection of his parents. Before the arrival of another infant the child should be shown the privileges and advantages of growing up. He should be taught to feed and dress himself as far as possible, and if he is to be moved out of the parents' room the transfer should be made several months before the new infant is expected. If the child is old enough, he may be told that a new baby is coming and that it will be his brother or sister. The helplessness of the infant may be emphasized and contrasted with his own self-dependence. If the mother goes to a maternity hospital, the child may resent her departure and blame the infant. This should be dealt with in a common-sense way before the mother-child separation takes place.

When properly handled, sibling rivalry in young children ordinarily diminishes in intensity. It may and often does, however, persist and may color the intrafamilial relationships permanently.

Treatment.—Parents must accept the child's spontaneous response of hate, resentment, and jealousy toward a new sibling as a natural result of the situation which confronts him. The child should be reassured of parental affection, and he should receive attention and privileges on a more mature level. The parents should see that he has affection and attention sufficient to make him feel secure in his new position, and they should avoid bestowing too much attention on the new infant in the older child's presence. Too frequently friends and relatives, in their eagerness to see the baby, unintentionally ignore the older child thereby hurting his feelings.

If the child is unusually jealous, the mother should avoid nursing or giving other care to the infant in his presence since the most frequent stimulus to hostile feeling in the older child is the sight of the baby being fondled by the mother. The mother must be careful, however, not to let the child feel that he is being excluded. The father should assume a more important part in the older child's life. In this way the child will receive additional affection and attention of a more mature type which will help to establish him in his new position of older brother or sister.

Where a nurse is employed, the parents should make sure that she understands that the older child is her responsibility as much as the younger, and they should choose someone who is interested and experienced in the care of older children. It is unwise for the mother to care for the infant and turn the older child over to the nurse entirely since this naturally increases the rivalry feeling.

In rare instances, where the jealousy is intense, it may be necessary to separate the older child from the infant to avoid bodily harm to the infant.

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Critical Review

THE ANEMIAS OF EARLY INFANCY

Pathogenesis and Diagnosis

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THIS presentation deals with the anemias of early infancy and is confined to that group which occurs in the newborn period. Since the latter embraces the period of adjustment to extrauterine life, its exact duration is variable and more or less arbitrary limits of from four to six weeks have been assigned to it.[1, 2] This is a time when the blood picture may be obscured by the effect upon hematopoiesis of profound alterations in various systems following birth and by the subsequent onset of changes incident to growth and development. In addition, the hematopoietic system of itself undergoes concurrent modifications. Anemia encountered in this period must, therefore, be interpreted in the light of these changes and with particular reference to the contemporary hematopoietic background. In this paper an effort will be made to reduce the number of primary blood diseases by a search for extrinsic forces peculiar to the newborn period and, as with older age groups, for possible intrinsic factors whose deficiencies create disturbances in hematopoiesis. Accumulating evidence points to the promise of eventually abandoning the differentiation between primary and secondary anemia and for justification of the view that "anemia is really more a symptom than a disease and is always secondary to some known or unknown cause."[3] With a better understanding of the hematopoietic mechanisms of this period and their aberrations it is hoped that a more adequate employment of available therapeutic agents may be achieved.

ANEMIAS OF THE NEWBORN PERIOD

In extending the scope of the newborn period, a wider variety of blood diseases is necessarily included. Chronologically the anemias of this period may be grouped into two categories. The first group appears in the earliest days of the neonatal period and includes the symptom complex designated as erythroblastosis fetalis, hemorrhagic disease of the newborn, and a miscellaneous group of anemias associated with sepsis and infection which includes congenital syphilis. The second group of blood dyscrasias belongs properly to later infancy, but cases have been reported of their onset late in the newborn period. The diseases of this group comprise the condition referred to variously as erythroblastic, Cooley's, or Mediterranean anemia, familial hemolytic jaundice, and hypoplastic anemia. Because of the limitation of this

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discussion to the blood disorders of the newborn period, hypochromic or nutritional anemia which occurs in later infancy will be omitted. Mention will be made, however, of the related congenital nutritional anemia which has been described by some authors.

Anemia in general represents a failure to maintain the equilibrium between red cell formation and red cell destruction. Blood destruction may be gauged by the level of bile pigments in the plasma and excretion of urobilin in the stools. The concentration of bile pigments may be readily measured by estimating the icteric index, and, when they are sufficiently elevated, jaundice constitutes a diagnostic feature provided liver damage and biliary obstruction can be excluded. Blood formation is measured by the percentage of reticulocytes, and constitutes a valuable guide to the effectiveness of antianemic agents such as iron and liver. Increased reticulocyte values are, however, also conspicuous in the hemolytic anemias provided the bone marrow is active and has not been rendered aplastic by the injury of the hemolytic agent. In deficiency anemias a reticulocyte response occurs, following the administration of antianemic principles, and rises from previous low levels, reaches a peak, and then falls. In the hemolytic anemias, on the other hand, reticulocytosis is elevated and sustained, prior to and without treatment, and represents an intensification of bone marrow activity. With a marked increase in the number of reticulocytes a small number of normoblasts may be observed in either process, but their appearance in excessive numbers indicates a disturbance in blood formation affecting maturation of erythrocytes.

A simple clinical classification of anemia is based on whether the anemia is due to increased loss of blood resulting from hemorrhage or accelerated destruction of red cells or is due to decreased blood formation from a deficiency of specific substances or depression of marrow activity by a variety of agents. The blood dyscrasias which occur in the neonatal period are difficult to classify accurately, not only because as in older individuals a specific anemia may manifest both hemolytic and hypoplastic features but because the blood picture at this time is influenced by the processes involved in postnatal adjustment which takes place in the blood and other systems.

ANEMIAS OF THE EARLY NEWBORN PERIOD: ERYTHROBLASTOSIS FETALIS

Among the blood dyscrasias of the newborn period none has afforded more interest in recent years as regards diagnosis and etiology than the symptom complex of erythroblastosis fetalis. The diseases comprising this group consist of hydrops fetalis, icterus gravis, and anemia of the newborn. Although they present a varied clinical picture, they are linked together by certain common features: namely, by severe grades of macrocytic and hyperchromic anemia, the fetal type of extramedullary hematopoiesis (erythroblastosis), by abnormal numbers of nucleated red cells in the circulating blood (erythroblastemia), edema, jaundice and by the fact that successive newborn siblings may be affected by one or the other of these conditions. Yellow vernix caseosa and amniotic fluid may presage the development of one of the forms of this disease, but the association is by no means constant. In both hydrops fetalis and icterus gravis the placenta, the liver, and the spleen are notably enlarged. In the former, edema is the most

striking feature while in the latter it is the intense jaundice, although both signs occur in each condition. In icterus gravis the reticulocytes are increased and in excessive numbers may reflect a tax on the regenerative capacity of the bone marrow to the point of a derangement in hematopoiesis. The latter was observed recently in a fatal case of icterus gravis in which, soon after birth and prior to transfusion, the reticulocytes measured 59 per cent. In severe cases of icterus gravis the nucleated red cells may reach levels of 50,000 and more per cubic millimeter and may not disappear from the circulation for several weeks.[4] This is in contrast with the normal values of newborn infants in whom the number of normoblasts in the first few days of life range from 1000 to 2000 per cubic millimeter, with 5000 per cubic millimeter as a physiologic maximum.[5] In icterus gravis the large number of nucleated red cells is often accompanied by an exaggeration of the normal leucocytosis present at birth and by the appearance of large numbers of immature cells of the myeloid series and occasionally even by myeloblasts. The features enumerated for the other members of the triad are possessed in least degree in the cases of anemia of the newborn. Here the anemia, which is sudden and severe, is noted at a variable time during the first two weeks; extramedullary hematopoiesis is inconstant, while nucleated red cells may be absent or only slightly increased and then not until the onset of recovery. An increased number of reticulocytes is sometimes observed at the onset and during recovery. Jaundice is mild or absent, and in the face of apparent hemolysis it is explained by the functional ability of the liver to excrete the bile pigments which have been formed. The gradation of one member of this group into another has been repeatedly demonstrated by cases of icterus gravis with severe edema, and by milder cases of this condition which, during the recovery phase, are almost indistinguishable from congenital anemia. It is frequently impossible to separate congenital anemia of the newborn from less severe cases of icterus gravis when the anemia in its early stages is associated with transitory jaundice and erythroblastemia. Among the more common conditions with clinical and hematologic pictures which resemble this group and which should be excluded are physiologic jaundice, congenital syphilis, congenital obliteration of the bile ducts, and sepsis with jaundice.

The views concerning the basic hematopoietic disturbances responsible for erythroblastosis fetalis have been conflicting. Among the etiological factors that have been proposed are a persistence or a defect of embryonal hematopoiesis, nutritional disturbance of the mother, a hemolytic agent or toxin associated with toxemia of pregnancy, a dominant mutation in the germ cells of one of the parents producing blood pictures of all grades of severity,[6] infection, an antigen-antibody reaction producing abnormal destruction of red cells and injury to the liver,[7] and a deficiency of factors which normally control hematopoiesis. The most controversial point is whether these anemias are primarily manifestations of an underlying abnormality or of a metabolic disturbance of erythrocyte production,[4] or whether they are fundamentally hemolytic in nature. According to the latter hypothesis the erythroblastosis and erythroblastemia represent a response to excessive blood destruction.[8] Analysis of the case reports of these conditions reveals that these two processes are so interwoven that it is often impossible to decide which process predominates.

DEVELOPMENT OF THE BLOOD IN THE FETAL AND NEWBORN PERIODS

As mentioned, a more fruitful line of approach is to interpret the features of this blood disorder, as well as those of other neonatal anemias to be described, in relation to hematopoietic processes that are current in the normal newborn infant. This involves a consideration of normal blood formation in the fetus, the changing blood levels in the newborn, transference of sites of hematopoiesis, the balance between hemolytic and antihemolytic forces, the influence of processes associated with maternal hematopoiesis and of extraneous forces such as growth of the infant and superimposed infection. It is probably because of the interplay of these intrinsic and extrinsic forces that there is encountered in early infancy the wide variety of blood pictures whose exact interpretation is at times so difficult.

A consideration of the basic features of blood development involves fundamental problems of a controversial nature, but for the purposes of this presentation only those phases need be emphasized about which there is more uniformity of opinion. Blood cells in the embryo arise from the mesenchyme and the first cells produced in the yolk sac become the primitive red corpuscles. Since the mesenchyme is widespread throughout the embryo, blood formation takes place at first from multiple sites, but eventually becomes specialized in certain organs. Accordingly, in the first five weeks blood formation occurs initially in the wall of the yolk sac and is then assumed by the mesenchymal cells throughout the human embryo. In the sixth week the liver sinusoids of man become centers of extensive red cell multiplication, and toward the end of the second month the spleen enters into this activity. In the second and third months the thymus, the mesonephros and the lymph nodes become additional foci of blood formation. While the bone marrow makes its appearance in the sixth week, it becomes a site of active hematopoiesis in the third month. During the course of fetal life all of these organs produce blood cells, with the major activity residing in the spleen and liver. From an examination of 36 human embryos, Knoll[9] found that red cells alone were in evidence in the blood for the first two and one-half months of intrauterine life. At the end of this time granulocytes made their appearance, then the lymphocytes at the beginning of the fourth month.

The substitution in evolution, according to Jordan,[10] of bone marrow for the spleen in blood formation finds its basis in the relatively larger area and more elastic nature of the bone marrow. He emphasizes the structural similarity of the bone marrow and spleen in providing an ideal environment for red cell and hemoglobin formation. In both there are nonanastomosing arterial capillaries emptying into a rich plexus of venous sinusoids in which, by virtue of sluggish circulation and blood stasis, a relatively high carbon dioxide tension develops, factors of primary importance in the elaboration of hemoglobin and also in the formation of the primordial red cell. The bone marrow at birth takes over the hematopoietic role of the liver and spleen but the potencies of mesenchymal cells or of their reticular derivatives in the connective tissues for blood formation persist throughout life. Thus, in an infant with icterus gravis hematopoiesis has been noted in the liver, spleen, thymus, adrenals, pancreas, and kidneys as late as two weeks following birth. In older infants and children, when the usual blood sites are strained, compensatory hematopoiesis occurs quite readily in the liver and spleen.

The blood-forming potencies of the mesonephros of the embryo were illustrated in a boy, 7 years of age, with erythroblastic (Cooley's) anemia after splenectomy. In this child bone marrow containing hematopoietic areas was found in the adrenals and kidneys. Jordan[11] has recently reported a case in a man of 63 years with adenocarcinoma of the prostate in whom erythrocytogenesis occurred in the liver and spleen.

In osteopetrosis, or marble-bone disease, the marrow cavity may be narrowed as a result of overgrowth of bone. The spleen, liver, and lymph nodes are often enlarged, and in many case reports compensatory extramedullary hematopoiesis has been noted in these organs at all age periods.

So active is the demand for blood cell formation that in the infant and young child all the bones are filled with red marrow. Fat appears in the long bones at about seven years of age,[12] and it is only with the appearance of the nonfunctioning yellow marrow that a potential reservoir is created in the bone marrow for blood formation in periods of stress. In early infancy, therefore, in the absence of reserve marrow, the additional demands upon hematopoiesis arising from anemia associated with infection or from specific blood dyscrasias may necessitate the reactivation of extramedullary fetal sites. Another compensatory mechanism consists of expansion of the marrow cavity by absorption and atrophy of bony trabeculae and of cortex. The changes in the bones may be sufficiently marked to be visualized roentgenographically, but they usually are not observed until later in infancy when the anemia has persisted for a considerable period. Erythroblastic anemia of the Cooley type has been known, however, to occur early in infancy. Caffey[13] cites a case of an infant in whom pallor was noted at the age of one month and in whom bone atrophy was observed by x-ray in the fourth month. These changes consisted of widening of the medullary canals with cortical thinning and were most conspicuous in the distal ends of the femora, giving them an appearance of fullness and of rectangular contour. As early signs he noted widening of the diploic space in the skull and a thickening of the lower portion of the frontal squamosa and of the horizontal plates of the frontal bone. These changes in the skull, in the long bones, and in the short tubular bones constitute an effort to provide additional sites of hyperplastic marrow and should be looked for in the roentgenograms of the young infant. These changes often serve as a valuable diagnostic aid, particularly when blood pictures are still equivocal.

It is apparent, therefore, that under stimulation the fetal blood-forming sites may become active at any age period, but more frequently in the young infant. It is also entirely reasonable to suppose that the bone marrow does not abruptly appropriate the hematopoietic activities of the liver and spleen with the interruption of the placental circulation, but that this transfer is a more gradual process extending over a variable period in postnatal life. In this respect it is analogous to the gradual closure of the foramen ovale and obliteration of the ductus arteriosus for several weeks after birth. Excluding the specific blood dyscrasias, the presence of immature red and white cells in the circulating blood of the newborn infant results from the influence of infection and hemorrhage upon blood-forming structures that have not entirely relinquished their fetal functions.

HEMOGLOBIN AND RED CELLS IN THE EARLY NEWBORN PERIOD

The increased hemoglobin and red cell levels found in the blood at birth have been regarded as a compensatory polycythemia resulting from a state of oxygen want in which the fetus lives. According to this concept, with the termination of anoxemia at birth the cellular increase is no longer required and destruction of the redundant red cells and hemoglobin occurs.

In recent years more detailed data of the blood elements in the neonatal period have been obtained from two sources: from a further investigation of the correlation between the concentration of hemoglobin and red cells and the incidence of physiologic jaundice, and as part of more extensive studies of blood formation of the normal infant. The results have shown that the depth of jaundice cannot be correlated with the level of hemoglobin or of red cells and that causes other than the excessive hemolysis must be sought for in the causation of physiologic icterus.[14, 15] Analysis of the blood examinations upon which these conclusions were based revealed the fact that, contrary to the usual conception, a sharp drop in hemoglobin and in the number of red cells does not occur early in the neonatal period. Bonar[16] states, for instance, that there was little change in the hemoglobin or erythrocyte levels on the third, sixth, or ninth day, a period when a rapid rise and fall of the icteric index occurred. It has been suggested that the increased bilirubin content of cord blood in the newborn infant may be ascribed to impairment or immaturity of the mechanisms provided for its elimination. Snelling[14] has pointed out that physiologic icterus occurs at a time when the liver is abandoning its fetal hematopoietic functions and when the portal circulation is increased, with a resulting temporary functional inability of the liver to excrete bile pigments. The hypothesis of liver insufficiency, however, has been recently challenged by Lin and Eastman,[17] who found that the infant at birth can excrete bilirubin after its intravenous injection.

The values reported in the second or normal group of infants also revealed only a slight reduction in red cells and hemoglobin in the blood of the newborn infant and confirm the view that a precipitate drop in red cells and hemoglobin does not occur in the normal infant in the first week or ten days of life. The sustained hemoglobin values are of particular significance because it is the destruction of this component of the red cells which leads to the liberation of pigment concerned with icterus. In a large series of cases Guest[18] found that the mean of the cell counts in cord blood samples was 4.8 millions, that during the first few days of life the number of cells tended to increase, and that after the first ten days the cell count diminished rapidly for two or three months. The hemoglobin in cord blood averaged 17.9 Gm. per 100 c.c.; from the first to the tenth day, 19.0 Gm.; and at two months, 12.1 Gm. In this series the hemoglobin in whole blood followed closely the changes in the red cell count, and there seemed to be no significant change in either of these values during the first ten days of life. Faxen's studies[19] showed an average value in the first twelve hours of 5,780,000 red cells and 23.2 Gm. of hemoglobin; and at seven days, 5,120,000 red cells and 21.7 Gm. of hemoglobin. The average hemoglobin value and red cell count at one month were 17.9 Gm. and 4,700,000 and at 2 months 13.5 Gm. and 3,910,000 per cubic

millimeter, respectively. Kato and Emery[20] also showed that during the first two weeks of life the average hemoglobin values were high, ranging between 17.7 and 18.7 Gm. per 100 c.c. of blood, and that the sharp and sudden drop does not occur until after the second week, reaching a low level of 10.5 Gm. in the third and fourth months. Waugh and his associates,[21] employing a photoelectric colorimeter technique, found that the average hemoglobin of newborn infants in cord blood was 15.36 Gm. per 100 c.c. of blood; on the second day it averaged 15.49 Gm. and on the sixth day 14.93 Gm. On the ninth day the hemoglobin value was 14.70 Gm., or a reduction of only 0.66 Gm. from the time of birth. In a recent study with a large series of premature infants, Magnusson[22] also observed high levels in the first week of life. The average hemoglobin and red cells on the first day were 126.1 per cent and 5,180,000 per cubic millimeter, and on the seventh day 123.9 per cent and 5,280,000 per cubic millimeter, respectively.

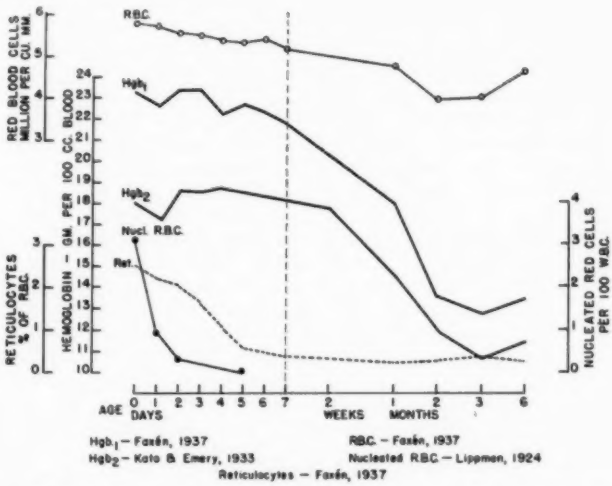

Fig. 1.—Blood levels in the newborn period. Note that the average decline in hemoglobin and red blood cells in the first week of life is only slight. The drop in nucleated red cells and in reticulocytes is more abrupt.

While dehydration may conceivably account for concentration of the blood elements directly after birth, it does not account for the high values observed during the entire first week or ten days of life. When the red cell and hemoglobin values are correlated with the serum protein content of the blood during this period, it has been observed that the concentration of the latter is reduced below the adult values and that the fluctuations are small.[23] The higher blood levels of the first few days of life may also be accounted for by a continuation of intra-uterine hematopoietic activity. This is suggested by the fact that the level of reticulocytes is increased at birth and for a short time thereafter, indicating augmented bone marrow activity. Faxen's values[19] for reticulocytes of 2.5 per cent at birth and the drop to about 0.5 per cent on the fifth day approximate those of other investigators. Normoblasts are also frequently observed in the normal infant

on the first day of life, but they usually disappear during the first week, in most instances from the third to the fifth day. The normal number of nucleated red cells varies according to different authors. Lippman[24] found the average number at birth to be 3.2 per 100 white cells, but in one case he recorded 37.8 nucleated red cells. In general, the average at birth may be stated as ranging from 3 to 10 per 100 white cells. Some of the values discussed in the text are illustrated in Fig. 1. It is interesting that though the hemoglobin curves of Kato and Emery from this country and of Faxen from Sweden reveal sustained blood levels in the first part of the neonatal period, the actual differences between the hemoglobin content of the blood in each series are noteworthy. This discrepancy has been noted previously in other investigations and has been ascribed to the climatic, racial, hygienic, and dietetic factors prevailing in particular localities and communities.

FETAL HEMOGLOBIN

Besides the elevated hemoglobin value and the polycythemia present at birth, another compensatory mechanism that has been described to combat fetal anoxemia is the presence in the fetus of a type of hemoglobin which is more resistant and has a greater affinity for oxygen than has adult hemoglobin.[25-28] Eastman, Geiling, and DeLawder[29] found that at gas tensions between 25 and 60 mm. Hg fetal blood absorbs oxygen more effectively and at all gas tensions releases carbon dioxide more readily than does the blood of the mother. Barcroft[30, 31] states that the greater affinity for oxygen of fetal than of maternal blood depends on the fetal type of hemoglobin, a type which acquires oxygen readily and sheds it with difficulty. The difference between the fetal and the adult types of hemoglobin has been located in the globin fraction of the hemoglobin molecule. Studies are not yet available which show the time and rate of removal of fetal red cells and hemoglobin from the circulation of the newborn infant. In the neonatal period, however, this resistant type of fetal hemoglobin is replaced by the normal or adult type, and it is conceivable that the drop in hemoglobin and red cells constitutes a means by which the newborn infant eliminates these residual products of fetal life.

MATERNAL AND FETAL HEMATOPOIESIS

While fetal hematopoiesis appears to proceed independently, there is suggestive evidence for the influence of factors derived from the maternal organism. In comparing the erythrocytes of the fetuses of many species with those of the newborn, Wintrobe and Shumacker[32] noted that during the course of fetal development these cells increased in number and decreased in size. In addition, there was a decrease in the number of erythroblasts and reticulocytes so that the composite picture resembled the sequence of events occurring in patients with pernicious anemia undergoing liver therapy. It was suggested by them that an antianemic factor normally found in the liver passed through the placenta to the fetus from maternal stores and that in certain instances these stores might be so depleted that serious blood dyscrasias might conceivably result. In the mother a pernicious type of anemia of pregnancy might occur, and in the fetus a deficiency of this substance might explain some of the anemias of the newborn. There have been few cases recorded in which macrocytic anemia in the mother has been attended by one of the group of erythroblastosis

fetalis in the infant. Ritter and Crocker,[33] however, have recently reported a case of severe macrocytic anemia during pregnancy, with delivery of an infant who showed the typical blood picture and clinical course of anemia of the newborn.

It has been stated that liver extract administered to mothers during pregnancy who previously had given birth to babies with erythroblastosis fetalis resulted in some instances in the subsequent birth of normal babies. Despite the lack of direct clinical application, these studies have nevertheless called attention to the nature of the hematopoietic activity occurring in the fetus and to the possibility that a maturation factor found in the liver may play a role in fetal hematopoiesis.

HEMOLYTIC AND ANTIHEMOLYTIC FACTORS

The drop in red cells and hemoglobin which ensues after the initial period of slight or moderate fluctuation may be regarded as an expression of a predominating hemolytic process. To offset its overactivity, the presence of restraining antihemolytic forces has been suggested analogous to those which maintain equilibrium in other systems. The relatively constant or moderately diminishing level of hemoglobin and red cells during the first week of life lends additional support to the belief of Hampson[34] that an antihemolytic substance supplied in utero by the mother restrains the hemolysis of fetal red cells and that this is still present in the blood of the newborn infant. The normal newborn infant is thus protected against sudden and explosive hemolysis as occurs in congenital anemia.

There is confirmatory evidence for this hypothesis from other maternal-fetal relationships. Anatomic studies have shown that the human placenta possesses a single layer of cells separating the maternal from the fetal blood so that placental transmission is more easily effected than in the type of animal like the ruminant which is provided with a complex placental structure. Many studies are available showing that the transfer of immune bodies and of hormones occurs readily through the human placenta. The transmission of hormone factors from the mother has been suggested as responsible for promoting the descent of the testes, of producing hypertrophy of the breast and secretion of milk in newborn infants of both sexes, and of producing the adult type of hypertrophied vaginal epithelium which is noted at birth.[35]

The antihemolytic factor which is produced by the mother and transferred to the fetus, as postulated by Hampson, and which is effective in the uterus and for a variable time after birth, therefore, represents more than a vague concept. Its presence has been given support not alone by the more recent studies which have been cited showing sustained blood levels in the early neonatal period but by the dramatic effectiveness of transfusions and of serum administration in erythroblastosis fetalis. Transfusion not only constitutes a form of substitution therapy by restoring the red cell and hemoglobin content of the blood and conceivably by supplying the antihemolytic factor, but it probably accelerates the elaboration by the infant of its own antihemolytic and maturation factors. In a previous study[36] it had been shown that isoagglutinins enter the fetal circulation by placental transfer from the mother, and at a variable period following birth the infant elaborates its own agglutinogen and associated isoagglutinin to produce individual and final blood groups. Transfusion

has been observed to accelerate this process in the young infant as illustrated by instances in which the blood groups apparently changed soon after this procedure. It is possible that frequent transfusions of small quantities of blood in erythroblastosis fetalis may serve the purpose of stimulation more effectively than larger transfusions at longer intervals.

FACTORS REQUIRED FOR NORMAL HEMATOPOIESIS AND THEIR RELATION TO ERYTHROBLASTOSIS FETALIS

As already stated, in cases of erythroblastosis transfusion tends to correct a deficiency of one or more factors required for normal hematopoiesis. The factors which control each phase of blood development extend from the earliest differentiation of cells from the mesenchyme of the embryo to changes in their size and number before birth. The hematopoietic principles that are operative in each of these phases in the fetus are probably similar to those required in comparable phases in the maturation of the erythrocyte following birth. Thus the low oxygen tension in the fetus which stimulates the mesenchyme to produce red cells serves also as the stimulus responsible for the mitosis of endothelial cells lining the intersinusoidal capillaries of the bone marrow to produce the earliest megaloblasts. Beyond this stage the erythrocyte-maturing factor found largely in the liver is required for the transition of megaloblast to normoblast, and iron, copper, vitamin C, and thyroxin are probably necessary for the final maturation of the erythrocyte. That the erythrocyte-maturing factor in liver may be insufficient in icterus gravis and anemia of the newborn is suggested by those cases whose final and complete recovery is expedited by the administration of liver.

In addition to these better defined factors, hemolytic and antihemolytic forces contribute to the maintenance of blood equilibrium. A substance found by Josephs[37] in the ether-insoluble fraction of the concentrated protein-free plasma which reduced the rate of blood destruction in sickle-cell anemia and in congenital hemolytic jaundice gives concrete evidence of the presence of an antihemolytic factor in blood.

It has also been suggested on the basis of experimental and pathologic evidence that interaction between the endocrines and the hematopoietic system regulates the orderly proliferation of the mesenchyme.[38] The multiplicity of factors, therefore, which control hematopoiesis is analogous to the number of pituitary hormones concerned with growth and maturity.

The clinical and hematologic manifestations of erythroblastosis fetalis may, therefore, be interpreted in part at least as disturbances of varying grades of severity due to deficiencies of one or more factors which normally regulate and assure the orderly processes of hematopoiesis. These principles normally originate in the fetus, continue to be elaborated in sufficient quantities in normal newborn infants, and are probably supplemented by a supply from the mother. Inadequacies of the latter component may explain the familial nature of this syndrome. Guest[18] observed successive cases of nutritional anemia in the siblings of two mothers. He called attention to the familial aspects of this disease, its predictability, and the progressive anemia in successive siblings. These observations are of primary importance in that they establish a basis for the familial character

of some of the blood conditions in early infancy, and it is probable that similar deficiencies may exist in other hematopoietic factors which may pass unobserved in the first-born but become more apparent in later pregnancies as the deficiency becomes more pronounced. In accordance with this hypothesis, erythroblastosis in successive pregnancies appears when inadequate contributions from the mother are further reduced by delayed elaboration of factors by the fetus or by the newborn infant.

It is possible, of course, that toxins, as suggested by De Lange,[39] which possess a special affinity for hematopoietic structures may account for the pathogenesis of erythroblastosis. This theory, however, as well as others including the explanation on the basis of deficiencies, still awaits more extensive investigation, particularly in the direction of the isolation of individual causative agents.

HEMORRHAGIC DISEASE OF THE NEWBORN

In addition to the disturbances in red cell maturation and in the forces controlling hemolysis, the factors involved in the clotting of blood may also be affected during the neonatal period. Into the category of hemorrhagic disease of the newborn should be placed those spontaneous evidences of bleeding that are associated with peculiarities in the clotting mechanism inherent in this age period. From it should be excluded hemorrhage due to birth trauma, the vomiting of blood from extraneous sources, bleeding from ulceration in the gastrointestinal tract, and that associated with sepsis or syphilis. Thrombopenic purpura may occur in the newborn in association with a similar condition in the mother, and it may also account for the hemorrhagic tendency of icterus gravis. From this group should also be excluded certain cases of vaginal bleeding which are not associated with the hemorrhagic diathesis, but which have been attributed to the withdrawal of estrogenic substance transmitted from the mother. This is analogous to the pseudomenstrual or withdrawal bleeding observed clinically following the cessation of estrogenic therapy.[40] Hemophilia usually does not manifest itself until later in infancy, and it is of interest that the same etiological factors have at various times been considered for this condition as for hemorrhagic disease. In hemorrhagic disease the clotting time may be prolonged, the platelets are normal in number, and the bleeding time is only occasionally increased. The frequent occurrence of hemorrhagic disease with normal blood coagulation has been pointed out in several series of cases. It is possible that in some cases a delay would be noted if the test were carried out with venous instead of capillary blood. As emphasized by Clifford,[41] however, a diagnosis of well-defined hemorrhagic disease should not be excluded because of the finding of normal bleeding and coagulation time values.

In hemorrhagic disease bleeding occurs quite suddenly from the gastrointestinal tract, as oozing from the umbilicus and by the escape of blood into the skin and from mucous membranes, from the urinary tract, vagina, into the nervous system, and bleeding into the peritoneum and abdominal organs. The associated anemia depends upon the degree of blood loss and in severe cases a normoblastic response may occur.

The tendency to bleed is the result of several factors which are operative in the neonatal period. Normally the coagulation time of the

blood is considerably prolonged in the first four or five days of life. Hemorrhagic disease of the newborn must depend, therefore, on some impairment in the coagulation mechanism which exaggerates this normal prolongation. Spontaneous bleeding which is characteristic of hemorrhagic disease frequently does not occur at birth, but from the second to the fifth day of life. In Capon's series[42] the average age of the infant at the time of onset of bleeding was 41½ hours and in Javert's cases[43] only 34 per cent showed clinical bleeding on the first day of life. The remaining cases were distributed over the rest of the week, with the largest numbers on the second, third, and fourth days. In recent studies the changes in the elements involved in blood coagulation during the period when hemorrhagic disease is prevalent have been investigated and have thrown light on the etiology of this condition.

Leslie and Sanford[44] have shown that, although the platelets are quantitatively normal in the early newborn period, they exhibit a qualitative resistance to disintegration early in life, a factor of importance in the inception of clotting. They found that the resistance to disintegration is increased until the fourth day of life and then decreases until the tenth day, when disintegration is greater than at birth. In two cases of hemorrhagic disease they found this platelet dysfunction was notably exaggerated.[45]

In a recent study Waddell and Guerry[46] pointed out that newborn infants manifest decided differences in the clotting time, that the prothrombin content of the blood as judged by the prothrombin clotting time was deficient in certain infants who were apparently normal, and that the most marked deficiency exists between 48 and 72 hours. They further found that the administration of a vitamin K concentrate to the infant reduced the prothrombin and blood clotting time. Hellman and Shettles[47] also found low plasma prothrombin levels at birth which were lower in the premature than in the full-term infant. These levels could be raised either by feeding vitamin K to the mother before delivery[48] or to the infant after birth. Brinkhous, Smith, and Warner,[49] by more direct measurement of the prothrombin level, found that in the newborn infant it varied between 14 and 39 per cent of the level of the adult plasma and rose to adult values about the end of the first year. In a case of hemorrhagic disease the plasma prothrombin was less than 5 per cent of the normal adult values. Owens and his co-workers,[50] using the same method, found that in the period between the second and sixth days of life there occurred a further fall in prothrombin value and that at the end of five to seven days there was a return to the value at birth. The studies suggest that hemorrhagic disease depends on an abnormal lowering of prothrombin levels which are already reduced. Bleeding does not occur more frequently, according to these authors, because of the rapid conversion of prothrombin to thrombin which compensates for the quantitative deficiency in this substance. In the pathogenesis of hemorrhagic disease abnormalities in capillary resistance as well as loss of integrity of smaller vessels produced during labor should also be considered.[43] It is possible that, in a certain group at least, vascular lesions constitute the immediate cause for the hemorrhage and that bleeding is maintained by diminished clotting of the blood.[51]

In addition to replacement of red cells and of hemoglobin, the favorable effects of transfusion in hemorrhagic disease may be at-

tributed to an increase of the thromboplastin of the "globulin substance" recently isolated from normal plasma,[52, 53] and of prothrombin. Transfusion also probably accelerates the production of these elements by newborn infants in whom it may be delayed. According to this hypothesis, it may be assumed that a more mature type of platelet is formed which disintegrates more readily to liberate thromboplastin.

ANEMIAS ASSOCIATED WITH INFECTION AND SEPSIS

A varied blood picture is observed in infection in the neonatal period, depending upon its severity. Since there may be a lag in the shift from fetal to extrauterine hematopoiesis, infection often results in a fetal type of blood picture with an outpouring of nucleated red cells and of immature white cells. The newborn infant with congenital syphilis may show this picture together with jaundice, anemia, an enlargement of the liver and spleen, and a tendency to hemorrhage. It must then be differentiated from icterus gravis, which it closely resembles, by serologic tests and roentgenograms of the long bones. Jaundice and bleeding may occur in the course of sepsis and, according to Dunham,[54] were more commonly associated with staphylococci and *B. coli* than with streptococci. Anemia, however, was more frequent with streptococcus and *B. coli* septicemia than in that caused by staphylococcus. Winckel's disease is a severe form of hemolytic anemia which is probably due to infection and is associated with cyanosis, icterus, and hemoglobinuria. The onset of this condition as well as of other forms of sepsis does not occur until about the third or fourth day of life or at a later day in the first two weeks of life.

CONGENITAL NUTRITIONAL ANEMIA

In accordance with the observations of Strauss,[55] it has generally been accepted that infants born of mothers who have suffered from iron deficiency during pregnancy showed a normal blood picture at birth and that the influence of inadequate storage did not become manifest until later in the first year. Parsons and co-workers[56, 58] and Neale and Hawksley,[57] however, have noted exceptions to this principle in the cases of nutritional anemia observed at birth or soon after, which were identical with nutritional anemia in older infants. These cases could be traced to maternal iron deficiency and possibly deficiency of other hematopoietic substances. These inadequacies could be sufficiently severe to produce typical iron deficiency in the mother, and in the case cited by Alt[59] a woman with a hemoglobin content of 6 Gm. per 100 c.c. of blood gave birth to an infant with a hemoglobin of 12 Gm. per 100 c.c. The infrequency of congenital iron-deficiency anemia despite a deficiency of iron in maternal tissues attests to the adequate transfer of hematopoietic substances from mother to fetus, sufficient at least in amount to tide the infant over the early period of insufficient iron intake.

With a history of pallor from birth, this form of anemia must be differentiated from other anemias in the neonatal period, particularly from members of the group of erythroblastosis fetalis. Congenital nutritional anemia, in contradistinction to the latter group, shows no jaundice, no sudden and pronounced drop in both red cells and hemoglobin, and reticulocytosis is absent before treatment is instituted. In addition, although the red cells may be moderately reduced, the reduction is usually in hemoglobin alone so that the anemia is hypo-

chromic rather than hyperchromic, as is the case in erythroblastosis fetalis. Furthermore, the administration of iron in congenital nutritional anemia results in recovery with an associated reticulocyte response.

The week or ten days following birth in which the hemoglobin and red cells are slightly or moderately decreased is followed by a period of rapid decrease in these elements. Josephs[60] regarded the uniformity with which these changes terminated at six weeks as evidence that this series of events took place uninfluenced by extrinsic causes. The fall in hemoglobin and in red cells is more rapid and the levels reached are lower in the premature than in the normal infant and more marked in the smaller and more premature infant. The rate of fall is subject to wide variations and is probably kept in check by controlling antihemolytic forces. The influence of the rate of growth and associated increases in volume upon the blood levels is not manifest at this time.[61] In the hemolytic process of this period the circulation is probably cleared of the remnants of fetal hemoglobin.

ANEMIAS OF THE LATTER PART OF THE NEWBORN PERIOD: FAMILIAL HEMOLYTIC JAUNDICE

During the latter part of the newborn period when hemolysis is in full progress, acholuric jaundice and erythroblastic or Cooley's anemia may make their initial appearance. Their clinical recognition in the early stages is attended with difficulty since they occur at a time of rapidly falling blood levels. In hemolytic jaundice the onset of jaundice may be delayed, and an anemia out of proportion to the lower physiologic blood levels may often be the first feature noted. High reticulocyte counts, so characteristic of the fully developed disease, may not be noted early but become progressively more prominent with the anemia. Even before the anemia is marked, the pathognomonic spherical red cells and the decreased resistance to hypotonic saline solution suggest the diagnosis of hemolytic jaundice. Hawksley[62] has reported a case in which increased fragility and diminished mean diameter were present at the age of 36 hours. The small, thick microcytes, staining deeply, stand out in contrast with the macrocytic cells so characteristic of the smear from the newborn infant. The general effect of the presence of these microcytes is to reduce the mean diameter of the red cells. Increased fragility of the red cells in hypotonic saline may be found in the baby, and in doubtful cases this test should be carried out with the blood of relatives in whom the disease may be latent.

ERYTHROBLASTIC OR COOLEY'S ANEMIA

In the early stages the blood smear of erythroblastic or Cooley's anemia shows few distinctive features. The large increase in nucleated red blood cells which characterizes the blood in advanced cases, particularly after splenectomy, is not observed early but makes an appearance as the anemia progresses. Experience with this disease emphasizes the extreme variability of the severity of the anemia from the time of onset. An unexplained leucocytosis in the latter part of the neonatal period accompanied by moderate numbers of immature myeloid cells may attract attention to the onset of this disease. The reticulocytes may be increased but not to the levels found in hemolytic jaundice.

The liver and spleen are not enlarged beyond that of normal infants, but in the course of the neonatal period a slight increase in size and firmness of the spleen is noted. The span of fragility of the red cells is prolonged, and resistance to extremely dilute concentrations of saline is noteworthy. It has been observed recently[63] that not alone is fragility of the red cells prolonged in the patient, but this property may be noted in adult relatives in whom the disease is latent and unsuspected.

With few exceptions[64] an important diagnostic feature of this condition has been its racial limitation to children, one or both of whose parents were born in Mediterranean countries. Its familial incidence may also serve to arouse suspicions of the disease in a later sibling. The characteristic bony changes produced by marrow hyperplasia and reflected in the roentgenogram are usually not observed for many months following the neonatal period when the anemia has become progressive. Similarly, the muddy yellow pigmentation of the skin and the mongoloid facies produced by changes in the skull bones are not observed until the anemia has persisted for some time.

In established cases of Cooley's anemia, in addition to erythroblastosis, the red cells manifest polychromatophilia, poikilocytosis, and anisocytosis. While variously shaped microcytes are present, the most important for diagnostic purposes are the macrocytic cells which appear in great numbers, and whose size is sometimes of unusual proportions. At least three types of macrocytic red cells characterize the blood of advanced cases of Cooley's anemia, especially following splenectomy, and one or more of these should be looked for in the smears of early cases. All types possess the fundamental characteristic of the red cells in this disease, namely, abnormal thinness. One of these is a nonspecific type and has been designated by Barrett[65] as a target corpuscle because of its deeply stained center and periphery arranged in concentric light and dark zones. He observed their development from bowl-shaped red cells in wet films and noted that they assumed a target appearance in drying and preparation of the film. He demonstrated that this type of red cell is resistant to hypotonic saline.

As observed in Fig. 2, *A*, the target corpuscle is a large cell and frequently the central dense, dotlike area is connected to the periphery by an irregular band of hemoglobin. It is nonspecific because it may be noted in a variety of conditions, notably sickle-cell anemia and obstructive jaundice. The second type of macrocyte (Fig. 2, *B*) is usually a round or sometimes slightly oval cell with a narrow rim of hemoglobin of varying thickness with a large area of central achromia in which a faintly stained island of hemoglobin may occasionally be discerned. This type of cell has been frequently observed in the blood of chronic cases of Cooley's anemia which may not have undergone splenectomy as well as in early cases. The third or most specific type is a large, pale erythrocyte, pointed out by Cooley,[66] which contains irregularly distributed hemoglobin which is clumped and whose intervening areas seem to possess staining defects. This cell (Fig. 2, *C*) is extremely thin and leaflike;[67] in wet preparations its edges are observed to fold over, and the several layers thus formed possess a remarkable transparency. Ridges are sometimes produced by wrinkling within the cell and together with scattered hemoglobin the cell assumes a peculiar appearance which typifies the disease.

To a lesser extent thin cells possessing some of the characteristics of these three cell types are also observed in hypochromic anemia, but they are associated with numerous achromic microcytes. When irregular hemoglobin distribution is noted, the cells are usually smaller and wrinkling is not observed. It must again be emphasized that the histologic features of the cells noted in Cooley's anemia are more distinctive when they appear in macrocytes, and this is very noticeable when blood films of this disease are compared with those of other anemias. In the early stages of Cooley's anemia, however, only a few of each or a single type of cell may be found, but their recognition aids in the diagnosis.

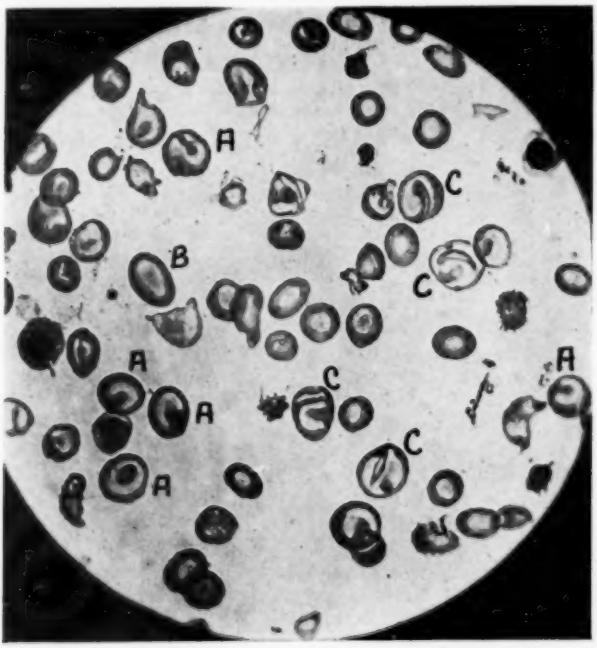

Fig. 2.—Blood smear in an established case of Cooley's anemia in a young child. Erythrocytes marked *A* are target corpuscles; *B*, macrocyte with large central achromic area and rim of hemoglobin of varying thickness; *C*, macrocytes containing clumped and scattered hemoglobin, with intervening unstained areas. The abnormal thinness is indicated by the ridges thrown up in various parts of the cells. Three nucleated red cells are also present.

The fragility test is of great importance in the diagnosis of both Cooley's anemia and acholuric jaundice. In congenital obliteration of the bile ducts, the jaundice and slight anemia may confuse the picture with that of hemolytic jaundice. The former, however, is an obstructive type of jaundice, and in this condition the red cells are frequently resistant to hemolysis in weak dilutions of saline as compared with the increased fragility of the red cells characteristic of acholuric jaundice. The increased resistance in obstructive jaundice is, however, not as marked as in severe cases of Cooley's anemia where hemolysis may not be complete even with distilled water.

Sternal aspirations may assist in clarifying the early diagnosis of hemolytic jaundice and of Cooley's anemia. At birth the erythroid elements in the smear from this material predominate, but in the course of the neonatal period these cells are gradually replaced by other myeloid elements so that the percentage of nucleated red cells in the smear reaches a level of about 25 to 30 per cent.[68, 69] The latter value is only approximate since normal data for each age period during infancy are as yet limited. Similarly, differential counts for sternal aspirations in suspected cases of Cooley's anemia and hemolytic jaundice in the neonatal period are as yet unavailable. Judging, however, from the findings in older infants and children, a persistence of high levels of nucleated red cells from birth or a further increase in their values to 50 per cent and over, lends confirmatory evidence to the development of these conditions.

HYPOPLASTIC OR CHRONIC CONGENITAL AREGENERATIVE ANEMIA

During the latter part of the neonatal period a form of anemia which resembles aplastic anemia may be noted. The clinical course and the blood picture, however, lack the severity and acuteness of this condition, and it has therefore been regarded as one of its variants to which the term hypoplastic anemia has been applied. The number of cases of this type of anemia is few, and they have recently been reported as a group by Diamond and Blackfan.[70] It is an aregenerative type of anemia, probably congenital, characterized essentially by a marked reduction in hemoglobin and red cells and is distinguished from aplastic anemia by its chronic course, by the absence of hemorrhage, and by the fact that the other cellular elements in the bone marrow may be only moderately affected or not at all. The platelets and the total number of leucocytes and reticulocytes are only slightly or moderately decreased, and the percentage of each type of white cell is normal. The smear shows an absence of immature white or red cells, and coagulation, bleeding time and clot retraction, and fragility tests are normal. Hypoplastic anemia should be considered when, despite adequate antianemia therapy, including frequent transfusions, hemoglobin, red cells and reticulocytes remain at low levels. This diagnosis is confirmed when the poor hematologic response persists for months and years following the neonatal period.

The first symptom noted is pallor, and in a patient brought to my attention[71] this was noted at one month of age. On physical examination a systolic murmur may be noted over the precordium, and the liver and spleen may not be enlarged. This anemia continues into late infancy and childhood and is not influenced by any form of antianemic therapy except transfusions which must be carried out at frequent intervals to sustain life. Bone marrow aspiration from the sternum reveals a marked reduction in the number of nucleated red cells as contrasted with the normal and with the increased numbers found either in erythroblastic anemia or in hemolytic jaundice. In the smear from the case which was mentioned, this decrease was noted, as well as an increase in the numbers of primitive cells and of eosinophilic leucocytes noted by other observers.[72] In this case the infant, now 19 months old, in whom pallor had been observed at one month, has been given transfusions at intervals of two and one-half to five weeks. Despite this and other vigorous antianemia therapy, the hemoglobin can

only be maintained at 29 per cent and the red count below two million cells. The white count is characterized by leucopenia with a more marked lymphocytic percentage than is normal for this age, and immature white cells and nucleated red cells have not appeared in the smears. The last bone marrow aspiration revealed only 1 per cent of normoblasts and 29 per cent of primitive cells.

The morphologic characteristics of these primitive or undifferentiated cells have been described by Sabin and her co-workers[73] and by Rhoads and Miller,[74] who found them increased in various forms of aplastic anemia. The latter authors as well as others[75] before them emphasized the wide variations in cytology of the bone marrow in aplastic or hypoplastic anemia and the lack of correlation between its cellular content and the peripheral blood picture.

The primitive cells, also designated by some as hematogones, are usually smaller than the ordinary lymphocytes but may resemble them in size and morphology so closely that it is necessary to compare smears from the bone aspirations with those from the peripheral blood while employing the same staining technique. These primitive cells are primordial blood forms which probably serve as ancestors for both erythrocytes and granulocytes. Cytologically they possess a dense homogeneous matlike nucleus and a narrow rim of nongranular basophilic cytoplasm. The nucleus, however, may be devoid of this cytoplasmic margin as is sometimes the case with normoblasts, but differs from the latter in its lighter staining property.

SUMMARY

The diagnosis of those anemias of early infancy which occur during the first four to six weeks of life was considered. This embraces the newborn period when adjustment to extrauterine life takes place. During this time profound alterations occur in various systems, including that of hematopoiesis. A satisfactory evaluation of the blood picture may be obscured by these changes as well as by the changes incident to growth and development.

The evidence presented in this paper points to the remarkable adaptation and integration of physiologic processes by which sudden and drastic shifts in blood levels are kept in check in the early newborn period. Recent studies reveal, for instance, that the hemoglobin level is usually sustained or shows only a gradual decline during this period. Similarly, the type of nutritional anemia which depends on maternal iron deficiency is of infrequent occurrence during the first days of life.

Adjustments in hematopoiesis may take place at varying rates of speed, and protective mechanisms may be upset. To facilitate the interpretation of the blood disorders of this period, normal blood formation and the forces which control hematopoietic equilibrium during fetal life and in the newborn period have been reviewed.

In the light of accumulating information, it is possible to relate some of the manifestations of the anemias of this period to deficiencies of one or more hematopoietic factors. Some of the features of erythroblastosis fetalis and of hemorrhagic disease may be explained on this basis.

Retarded elaboration of essential hematopoietic principles by the young infant probably contributes to the pathogenesis of a blood

disorder. In addition to its other functions, transfusion may serve as an accelerating influence in the production of these elements by newborn infants.

Since erythroblastic or Cooley's anemia, familial hemolytic jaundice and hypoplastic anemia may make their initial appearance during the latter part of the newborn period, it is important to look for certain hematologic features by which these conditions may be recognized.

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NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

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Panel Discussion on Chemotherapy

Chairman: Alexis F. Hartmann, M.D., St. Louis
Assistants: Henry L. Barnett, M.D., St. Louis
E. K. Marshall, Jr., Ph.D., M.D., Baltimore
Philip A. Shaffer, Ph.D., St. Louis
William B. Wendel, Ph.D., Memphis

Mode of Action of Sulfanilamide and Sulfapyridine

E. K. Marshall, Jr.

I do not feel that I should open this topic because after three years of intensive work I know practically nothing about the mode of action of sulfanilamide. A year ago, in a review on sulfanilamide I stated that no satisfactory explanation of the mechanism of action had been found. Dr. Shaffer in a recent paper said in connection with this statement that certain facts have been known for some time which appear to point plainly enough in the direction of a logical explanation. May I reaffirm here that despite Dr. Shaffer's enthusiasm for an oxidation theory of action, I still feel that no satisfactory explanation of the mechanism of action has yet been found.

In considering the mode of action of any chemotherapeutic agent, the interrelation of three factors is involved, namely, host, infecting organism, and drug. In connection with sulfanilamide the drug-bacteria factor involves the question of bacteriostasis, bactericidal action, and neutralization of toxins. The host-bacteria factor would consist of the response of the body defenses, namely, antibody production, mobilization of phagocytes, and phagocytosis of the bacteria; the host-drug factor would involve any change which the drug might undergo in the host to render it more effective as a bactericidal agent.

Numerous experiments have been carried out on the bacteriostatic and bactericidal action of sulfanilamide and to a less extent of sulfapyridine in vitro. Without going into details one can say that it is clear from these experiments that the result which is obtained depends upon many factors. Among these are strain of organism used, the size of the initial inoculum, the composition of the media, and the temperature at which tests are carried out. Thus, we find reports by different workers of concentrations of sulfanilamide which can be attained in the blood of patients exhibiting no effect, in vitro upon streptococci, but a bacteriostatic or a bactericidal effect in the patient's blood. The addition of a drop of blood to a tube of broth or a drop of broth to a tube of blood decreases markedly the bactericidal effect of sulfanilamide. A rise of the temperature at which the test is carried out from 37 to 39° C. may increase the activity of sulfanilamide and sulfapyridine in vitro 100 times.

There has been as yet no conclusive evidence of the stimulation of the activity of the body defense mechanisms although many observers have shown that phagocytosis of the bacteria which are injured or inhibited by sulfanilamide appears to play a definite role in the cure of an infected animal. Admitting that the drug can bring the infection under control, but that it requires the cooperation of the host's defense mechanism to eradicate the infection, the question arises what does the drug do to bacteria and how does it do it? Does the drug itself act or is it changed by the host or the bacteria?

Four theories which have been talked about recently in connection with the drug's mode of action will be discussed briefly.

The first theory is that proposed by Levaditi that sulfanilamide forms some sulfur protein complex which interferes with the nutrition of the bacteria and independently elaborated by Lockwood in the form that the drug acts on bacteria to prevent them from utilizing substrate or on the substrate to prevent its use by bacteria. Lockwood found that sulfanilamide in human serum killed streptococci but, if a small amount of peptone was added to the serum, the organism was protected from the action of the drug. Weld and Mitchell found that such clean-cut results were not obtained when rabbit serum was used and also found that although peptone might inhibit the action of sulfanilamide when very small inoculums were used at 37.5° C., when the tests were carried out at 39° C. the addition of peptone to rabbit serum actually increased the action of sulfanilamide. It is obvious that the simple theory of Levaditi and Lockwood will not explain the facts.

In regard to the theory of neutralization of toxins by the drug, I have little to say. Somewhat contradictory results have been obtained by various workers, and it is essential to get the facts straight before one can try to weave them into the general scheme.

Mellon and co-workers have proposed a theory that some substance formed from sulfanilamide acts as an anticatalase and allows the accumulation of hydrogen peroxide, which acts bactericidally upon the bacteria. Without going into a detailed description of this theory, I might point out that Fuller and Maxted showed that type 3, group A, β-hemolytic streptococci failed to produce hydrogen peroxide and that both the Richards and C 203 strains which are easily affected by sulfanilamide belong to this type. This is a bad snag in this theory.

We now come to the hydroxylamine theory of Mayer which has been recently elaborated in a more extended form by Shaffer. I should like to discuss this theory more fully, as we have been doing work on the hydroxylamine theory for over two years. While there are many facts which apparently do not fit in with an oxidation theory, it appears to me that investigations should be pushed in an attempt to obtain definite evidence for or against the theory. Mayer believed that sulfanilamide is oxidized in the body to p-hydroxylaminobenzenesulfonamide and that this is the active substance in sulfanilamide therapy. In support of his theory Mayer found that hydroxylamine in vitro was 100 times more bactericidal than sulfanilamide and acted without a latent period; that it converts hemoglobin into methemoglobin, thus explaining the frequent appearance of this pigment in the blood of patients treated with sulfanilamide and that p-nitrobenzenesulfonamide was inactive in vitro, but five to six times more active than sulfanilamide in vivo (the nitro compound being presumed to yield hydroxylamine more readily than the amine). The hydroxylamine was found to be no more active than sulfanilamide in the mouse infected with streptococci, but Mayer considered this as due to its rapid decomposition by the blood pigments and that conditions were quite different when hydroxylamine was found formed from the amino or nitro compound in the immediate vicinity of the bacteria.

From work which we have done, it seems that Mayer may have overestimated the activity of hydroxylamine compared to sulfanilamide in vitro and that the nitro compound when tested in vivo by an accurate method against sulfanilamide is of about the same order of activity and is not five to six times as active. It is true that the hydroxylamine forms methemoglobin almost instantly when added to blood and its formation from sulfanilamide may explain the methemoglobinemia which so frequently occurs. Shaffer in a recent article has summarized the facts which he thinks are conclusive evidence that the action of sulfanilamide is due to an oxidation product formed from it by atmospheric oxygen under the catalytic influence of respiring tissues or organisms. He states that the drug is without effect on the growth of bacteria in the absence of oxygen. This fact, however, is disputed by competent observers, and it has been shown that sulfanilamide is effective in vitro against facultative anerobes such as *Cl. welchii*. Mention is made of the well-known lag in the action of sulfanilamide. This has been confirmed frequently, and it is true that the hydroxylamine acts without a latent period. The frequent formation of methemoglobin in the blood of patients is also noted, but I should like to point out that streptococcus infections in dogs can be favorably influenced by sulfanilamide and no methemoglobin can be detected in the blood.

Fuller, at the recent International Congress of Microbiologists in New York, reported in the discussion of a symposium on bacterial chemotherapy that he had isolated from the urine of patients receiving sulfanilamide p-acetylhydroxylaminebenzenesulfonamide. If this observation is correct, it would prove conclusively that some sulfanilamide is converted into the hydroxylamine derivative in the human organism, but it does not by any means prove that this oxidation product of sulfanilamide is the active substance in therapy. It is difficult to see how the hydroxylamine derivative of sulfanilamide can act in the presence of blood. When this hydroxylamine derivative is injected intravenously into dogs, it appears to be completely changed to sulfanilamide in less than five minutes. Hydroxylamine may be the active substance in sulfanilamide therapy only if one assumes that it is formed on the surface or within the bacteria and acts immediately. This conception, however, is going to be extremely difficult either to prove or to disprove.

Mode of Action of Sulfanilamide and Sulfapyridine

Philip A. Shaffer, Ph.D.

In the early experimental work with the azo dye prontosil and later again with sulfanilamide, it was found that the drugs have little or no direct bactericidal effect on bacteria in vitro. Although later workers have observed occasionally a bacteriostatic effect on certain strains in vitro when quite small inoculants are used, such effects are not found when abundant growth is once established; and it appears to be difficult to demonstrate with sulfanilamide any marked effect in vitro corresponding to its action in vivo. As pointed out by R. L. Mayer in 1937, this discrepancy would seem to mean either that the drug somehow stimulates the "defense reactions of the body" or that the drug is converted in the body (more readily than in vitro) into some other bactericidal substance. Mayer adopted the second view and further supposed that the appearance of methemoglobin is due to the same derivative of the drug that causes the antibacterial therapeutic effect. The special significance of this point is that methemoglobin is the oxidized form of hemoglobin and is produced by active oxidizing agents (not by oxygen). It is therefore inferred that the active substance in the body is an oxidation product of sulfanilamide. And Mayer showed that one of the probable oxidation products, the corresponding hydroxylamine is markedly bactericidal in vitro, a fact which strongly supports his hypothesis. Nevertheless, Mayer's ideas have not received much acceptance by other workers in this field.

Being impressed by Mayer's reasoning, we undertook the study of the products of the oxidation of sulfanilamide and related substances with the object of learning which have definite bactericidal action and what parts of the molecule are responsible for the therapeutic effect. If investigations of this sort lead, as I believe they may, to an understanding of the mode of action of this type of chemotherapeutic agents, from such knowledge it should be possible to find even more effective drugs than those now available for infectious diseases.

The study of the oxidation products of sulfanilamide and sulfapyridine, curiously enough, takes us back to the very beginning of dye chemistry, to the work of Perkin in England, who isolated the first aniline dye from the products of the oxidation of aniline, and thus inaugurated the whole of modern dye chemistry. By this round-about route the present rapidly expanding subject of chemotherapy must be recognized as confirming the faith of Ehrlich in the therapeutic value of dyes and their derivatives.

The following evidence may be cited in support of the view that sulfanilamide and similar drugs act by being oxidized to bactericidal substances by the action of respired oxygen under the catalytic influence of respiring cells. In therapeutic concentrations bacteriostatic and even bactericidal action on certain strains of organisms can be demonstrated in vitro under aerobic but not under anaerobic conditions. Molecular oxygen, catalyzed by tissues in ways not now understood, is essential. The oxidation products, formed by treatment of the drugs with oxidizing agents in vitro are markedly bactericidal, as the drugs themselves are not. The oxidation products in vitro rapidly convert hemoglobin into methemoglobin. The part of the molecule which is capable of oxidation is the amine group. When this group is bound as in the acetyl compounds, the drugs are no longer oxidizable by chemical reagents, and they also lose their therapeutic activity more or less completely. A portion of that administered to human patients and to certain animals is excreted in the acetylated forms. The reverse change also occurs in the body; my associate, Dr. Kohl, finds that when acetyl compounds are fed or injected, or are treated with tissue hashes, a considerable fraction is de-acetylated, thus liberating the oxidizable form. The fraction varies with different substances. The first products formed by oxidation of the aromatic amine group are themselves powerful and reactive though highly unstable oxidizing substances. We have measured approximately their oxidation intensity and potentials but have not succeeded in identifying the radical-like substances. The level of intensity is considerably higher than that of iodine and benzoquinone, for example, and is comparable to that of other highly active oxidizing antiseptics. The hydroxylamines, on the other hand, are reducing agents and highly reactive ones. They react rather rapidly with oxygen and in doing so also become (or form) strong and active oxidizing agents which have bactericidal action, provided the culture does not contain an excess of other reducing substances which spare and protect the bacteria. It is our belief that the therapeutic activity is to be accounted for by this type of chemical reaction, resulting from the oxidation of the amine group.

How can one explain the undoubted specificity of these drugs? Why is sulfanilic acid so little effective as compared with sulfanilamide, the only chemical difference being the absence of an amid on the sulfonic acid? Why is sulfapyridine more effective with the pneumococcus? No one knows the answers, but it would seem to be due to diffusibility into or affinity for bacterial cells depending upon polarity of the drug molecule and the nature of the groups on the sulfonic end of the benzene ring. From this point of view, the future development of bacterial chemotherapy would seem very full of promise both for the discovery of new useful drugs and for providing investigators with fascinating and fundamental problems.

DR. MARSHALL.—I agree perfectly with Dr. Shaffer that at 39° C. one can demonstrate bactericidal reaction. However, when Dr. Shaffer says that sulfanilamide is not active without oxygen, I think it is necessary to bring together the conflicting opinions. There are observers who have found that it is active without oxygen.

As regards the methemoglobin formation, I admitted in what I said that if hydroxylamine is formed in the body from sulfanilamide, it probably forms methemoglobin as an oxidation product of sulfanilamide. It is curious that nobody has correlated the degree of formation of methemoglobin with the effectiveness of the drug in a patient.

CHAIRMAN HARTMANN.—It is a well-known fact that some patients get blue when they receive sulfanilamide. What is that due to? What is its significance? Should we do anything to prevent it? And what can we do about it? As you know, the literature has been a battleground concerning these new substances, and we will listen with respect to Dr. Wendel as he tells us of the cause of cyanosis when these drugs are used.

Methemoglobinemia as the Most Common Cause of Cyanosis in Patients Receiving Sulfanilamide

William B. Wendel, Ph.D.

Nearly all persons receiving sulfanilamide in doses sufficient to yield a blood sulfanilamide concentration of 4 mg. per cent show methemoglobinemia. The abnormal pigment can be detected in the blood of such patients within a few hours after the customary initial dose. The concentration of methemoglobin increases along with the sulfanilamide and usually reaches a maximum shortly after the blood sulfanilamide concentration becomes steady. It then remains essentially constant as long as the blood sulfanilamide level is maintained. Following withdrawal of the drug, the methemoglobin concentration decreases as the sulfanilamide is excreted. The degree of methemoglobinemia in most patients on the usual regime amounts to only about 10 or 15 per cent of the total pigment and, thus, probably is of no consequence. Not infrequently, however, a patient shows a 30 or 40 per cent loss in oxygen capacity due to methemoglobin formation. Such a loss of functional pigment may not be unimportant in a person with *normal* red cell count. It is probably a serious matter in an *acutely ill anemic* person. A methemoglobinemia of 50 per cent probably contributed to the cause of death of a patient in the John Gaston Hospital in Memphis recently.

The statistical studies of Harris and Michel suggest that infants and young children show a greater degree of methemoglobinemia at a given level of blood sulfanilamide than do adults. Hartmann, Perley, and Barnett have noted higher methemoglobin levels in their more acutely ill patients.

The fact that the concentration of methemoglobin may remain constant for several days while a given level of sulfanilamide is maintained in the blood does not mean that methemoglobin formation has ceased. Methemoglobin is reduced to hemoglobin in the human being at the rate of 1 to 1.5 volumes per cent per hour. The maintenance of a constant concentration of methemoglobin in the blood, therefore, indicates that the pigment is being formed at an equal rate. Thus, all of the blood pigment would pass through methemoglobin in 12 to 18 hours, and a disastrous loss of oxygen-carrying capacity would result within a few hours of giving sulfanilamide if it were not for constant reconversion of methemoglobin to hemoglobin. Enzyme systems within the erythrocytes carry on this important function. Recently it has been found that the rate at which methemoglobin is normally reduced to hemoglobin is only a fraction, perhaps one hundredth, of the potential

rate. For instance, a dog which has suffered a 50 per cent loss in oxygen capacity of the blood due to methemoglobin formation from intravenous injection of sodium nitrite converts all of methemoglobin to hemoglobin within 5 or 6 hours. Intravenous injection of 10 mg. of methylene blue per kilogram body weight just after the peak of methemoglobinemia shortens the time to 5 or 10 minutes.

This property of methylene blue of hastening conversion of methemoglobin to hemoglobin was first discovered in 1923 by Williams and Challis of Rochester, N. Y., and Steele and Spink of Boston. Patients who had been poisoned by aniline, acetanilide, and para bromaniline were said by these workers to be dramatically revived by intravenous methylene blue. Their reports, appearing at a time when others were emphasizing the fact that methylene blue brings about the reverse transformation, were received with skepticism. Several years later this property of methylene blue was again encountered in animal experiments by Hanschild and me. Clinical studies by Dr. Hartmann and his associates of Washington University and Dr. Gilbert Levy and associates of the University of Tennessee have shown that intravenous injection of 0.1 to 0.2 c.c. of 1 per cent methylene blue causes rapid disappearance of methemoglobin from the blood of patients receiving sulfanilamide. Several hours after such an injection of methylene blue methemoglobin usually reappears and may reach the preinjection concentration in from 12 to 24 hours. Thus, it may be necessary to repeat the injection every 6 to 12 hours if the methemoglobin concentration is to be kept low. In many cases the dye is effective, also, by mouth. By the oral route the action is slower, and much larger doses are required.

The extent to which methemoglobin accounts for the cyanosis frequently seen in patients receiving sulfanilamide has been a controversial subject. The occasional occurrence of sulfhemoglobin is not disputed. A very slight production of sulfhemoglobin produces marked cyanosis. Dr. Marshall and his associate Walzl do not believe that the small amounts of methemoglobin which they found in the blood of some of their patients could account for the cyanosis which the patients showed. They have suggested that aniline black may be the agent responsible for the dark color of the blood and the cyanosis. Later, Ottenberg and Fox offered a similar explanation. The latter workers attributed the cyanosis to colored derivatives of sulfanilamide which are formed when dilute solutions of the drug are exposed to ultraviolet light. The speaker has determined the spectral characteristics of the abnormal pigment in the blood of a number of patients showing varying degrees of cyanosis which could not be accounted for by cardiovascular or pulmonary abnormalities and finds them to be quite similar to those of methemoglobin, and unlike those of the colored derivatives of sulfanilamide described by Ottenberg and Fox. Recently, with Dr. John Hughes and Dr. James Hughes of Memphis, I have had the opportunity of studying thirty-six patients who were receiving plasmochin. As little as 5 to 10 per cent methemoglobin is frequently associated with easily recognizable cyanosis in such cases. This is especially true if the red blood cell count is below normal, as was the case in most of these patients.

Sulfapyridine produces cyanosis much less frequently than does sulfanilamide. At least this is true of the dose now commonly used. When methemoglobinemia does occur it is less severe.

In conclusion, I should like to mention a possible diagnostic use of methylene blue which was first suggested to me by Dr. Newton S. Stern of Memphis. Methylene blue might occasionally be useful in determining the cause of a sudden development or intensification of cyanosis in a patient receiving a drug known to form methemoglobin. If the cyanosis is due to methemoglobin, it will be dissipated by intravenous administration of methylene blue. If the cyanosis is due to cardiovascular or pulmonary involvement, methylene blue will have no effect. In this connection it should be mentioned that the dye will not affect the cyanosis due to sulfhemoglobin.

DISCUSSION

CHAIRMAN HARTMANN.—I anticipated this commendable modesty on the part of Dr. Wendel and, thinking that seeing is believing, I brought with me a little colored film of an infant becoming very cyanotic due to methemoglobinemia, which shows the effect of methylene blue.

We should say more about the significance of this condition. Suppose we are dealing with a gravely ill child; that child has a pulmonary involvement, a heart which is weakened, and perhaps at the beginning of the infection but a mild degree of anemia. During the course of his infection he becomes more anemic. Let us say that the original hemoglobin of 12 grams dropped to 9 grams. Then suddenly, due to sulfanilamide and particularly due to sulfapyridine because of a slight delay in the appearance of methemoglobinemia, 40 per cent of the remaining hemoglobin becomes nonfunctioning so far as oxygen carrying is concerned, and we have then only 5 or 6 grams of oxygen-carrying hemoglobin. I disagree with anyone who says that in such an instance the cyanosis is of no clinical significance. Such cyanosis would be dangerous to that patient. It throws an added load on him and may determine whether or not he is going to recover.

The other points of Dr. Wendel's were good. Sometimes it is not too easy to decide whether the cyanosis is of cardiac origin or pulmonary origin or is due to pigment. You can rule out methemoglobinemia by the therapeutic test he outlined. If it is due to methemoglobinemia, you have to wait only thirty minutes after injection of methylene blue.

Since this is a point about which there might be further discussion, I would like to ask if the other members of this panel would like to comment on this phase of the study.

DR. MARSHALL.—When the cyanosis from sulfanilamide was first observed, it became extremely important to decide whether the drug should be stopped or not. Our interest in methemoglobinemia arose from that practical consideration. I know very little about methemoglobinemia. In seven or eight patients who were clinically cyanotic, we took blood and compared the oxygen capacity with total blood iron. In some cases we also did spectrometric examinations and determined the active oxygen by the carbon monoxide method and reduced any methemoglobin that might be present. In two of these cases methemoglobin was definitely present. In the other five there was no difference between the oxygen capacity determined from the total blood iron and that after aerating the blood. This led us to publish a short note that cyanosis was of no importance and did not necessitate cessation of the drug and that methemoglobinemia might not be or probably was not the only cause or the main cause of such cyanosis. Since then we have done a little work on the problem. One difficulty we have met is the difficulty in producing a methemoglobinemia in animals from sulfanilamide. Recently it has been produced in chickens and in mice. In chickens, using the same method as in humans, it was easy to show that cyanosis was entirely accounted for by methemoglobinemia. In mice we could not find methemoglobinemia. In every instance sulfhemoglobin was present.

As regards the human being, it seems to me that it is quite clear that methemoglobinemia occurs much more frequently than we supposed. It may occur in some degree in every patient receiving sulfanilamide. In many cases it is the sole cause of cyanosis. However, there is a residual number of cases where I think it cannot explain the cyanosis. It takes 5 to 10 per cent of methemoglobinemia to give cyanosis. Many investigators have found, by comparing the total blood iron with the active hemoglobin, that there is no methemoglobinemia. It seems the situation we have in humans is that methemoglobinemia may occur in all cases and in some may be causative of cyanosis, and in others I feel that the traces

of methemoglobinemia are insufficient to account for the cyanosis. I feel that in most cases the cyanosis is of no importance and that it is no indication to stop the drug where severe infection exists. There are cases where methemoglobin rises to 37 per cent; that is dangerous and something should be done in such a case.

CHAIRMAN HARTMANN.—I think that is a fair statement of facts as they are now. I would like Dr. Wendel to tell us whether we can prevent the formation of methemoglobinemia as well as cause its rapid reduction; whether we can do the same with methylene blue in the case of sulfhemoglobin which also fails to carry oxygen and is much more stable and, when present, lasts for weeks. Dr. Wendel mentioned that sulfhemoglobin is not in great concentration in man and for that reason is not of great significance. But might one possibly prevent sulfhemoglobin from appearing?

DR. WENDEL.—A recent paper from England said that methylene blue would not prevent sulfhemoglobin from appearing; the details were not given.

There is one question regarding methods about which I should like to say a word. In a recent book on sulfanilamide the statement is made that one cannot determine the total hemoglobin of the blood accurately by the Newcomer or Sahli methods, if the blood contains methemoglobin, which means that most determinations of hemoglobin are no good. This statement is based upon one observation made by Stadie a number of years ago. I do not think it is true. His study concerned largely the methemoglobinemia produced by the addition of potassium ferricyanide. Methemoglobin formed by other methods does not change the values given by the Newcomer or Sahli methods.

CHAIRMAN HARTMANN.—I am supposed to know something about acidosis and alkalosis, and you can imagine my chagrin when almost the first good word said in the literature about the therapeutic action of sodium lactate was said in reference to what happens after sulfanilamide administration. I do not believe sulfanilamide causes acidosis. I do not believe that alkali should be given prophylactically, and I should like to show you why.

When sulfanilamide does produce a change in man, the change apparently is this: There occurs first primary stimulation of respiration. This primary ventilation leads to a blowing off of carbon dioxide, increase in alkalinity of the plasma which is compensated for by excretion of bicarbonate in the urine which then permits the pH of the blood to return to normal.

In this first slide we see these changes chronologically in the human subjects. Here is a subject who had a strongly acid urine before sulfanilamide was given, and you note that quite promptly after sulfanilamide administration the pH of the urine rose, due to the excretion of bicarbonate in the urine. The carbon dioxide content, which is largely a measure of bicarbonate in the blood, falls for a while and then levels off. By that time the pH of the blood is again falling towards normal, and the urine ceases to be as alkaline as it was previously.

If we use the ingenious charts of Hastings, we see, as far as the four primary paths of plasma displacement are concerned, that the carbon dioxide deficit type of alkalosis is in the direction of four o'clock, whereas the base bicarbonate deficit type of acidosis would be out in the direction of eight o'clock. If we take a normal subject and give him a single large dose of sulfanilamide, you see this type of change: In one instance very little change was noted; another showed the characteristic change out into the zone of carbon dioxide deficit alkalosis, and in the next slide we have almost the same changes in two subjects being treated for disease. When you give large doses of sulfanilamide and carry on this administration for a longer time, note how far the displacement of the acid-base balance

occurs. If you stop the drug, there is good compensation again. Compare that type of movement with what you see in regard to base bicarbonate deficient acidosis as it occurs in renal insufficiency; such cases fall in the zone of base bicarbonate deficient acidosis.

The next slide shows the same thing in a baby whose only renal trouble was inability of the tubules to reabsorb bicarbonate.

In order to test whether or not sulfanilamide rendered the renal tubules incapable of reabsorbing base bicarbonate, we produced an acidosis with ammonium chloride, then gave sulfanilamide, and we did not see a swing from acid to alkaline urine, which means that when real acidosis is present the tubules can reabsorb bicarbonate despite sulfanilamide. You can easily imagine that a real acidosis might be superimposed upon this first change because we are dealing with infections which often produce acidosis and sooner or later someone will find a real case of acidosis, but if you analyze it this way you will find the acidosis is produced by the infection and that the effect of sulfanilamide was as we showed on these slides.

DR. MARSHALL.—The early patients treated with sulfanilamide showed certain clinical symptoms of acidosis, and we carried out a few experiments upon normal dogs in which it seems to me the results were clear-cut.

First we attempted, on account of the alkaline urine present, to see if sulfanilamide would stimulate respiration or cause hyperventilation. We failed to find any effect upon respiration. We then found that by giving very large doses we got the picture of a decreased bicarbonate in the blood, a decreased pH, and an alkaline urine which seemed to me only to be interpreted as acidosis due to alkali loss by the kidney. Dr. Hartmann's results give exactly the opposite interpretation in human beings.

I have not made any examinations in human beings, but I would like to ask this question: Can you demonstrate in man that administration of sulfanilamide increases ventilation? I ask that because the only other work on the subject in patients where the various factors have been studied has been done by Bauer. This work is not published but is reported in Long and Bliss's book. Bauer took normal medical students and measured the ventilation; he measured the pH of the blood and bicarbonate of the blood, and the pH of the urine. He then gave sulfanilamide and found, during the first period, no change in ventilation but a decrease in pH of the blood and a decreased bicarbonate and an alkaline urine. It was a clear indication of acidosis. In the second period there was an increased ventilation due to some factor in the acidosis stimulating the respiratory center.

Clinical Comparison of Sulfanilamide and Sulfapyridine

Henry L. Barnett

The remarkable results of sulfapyridine therapy in pneumococcus infections which were first obtained and reported by Whitby, Evans, and Gaisford, and other British investigators seem quite regularly to have been duplicated by most subsequent workers in the field of bacterial chemotherapy. The undoubted superiority of sulfapyridine over sulfanilamide in the control of pneumococcus infections immediately raises the question as to whether or not a similar superiority exists in other infections, or whether the combined use of the two offers more in certain instances. Without going into detail concerning specific infections, I should like to review briefly the use of these drugs in the general bacterial infections caused by the various microorganisms, and to point out only those specific infections in which, at the present time, one seems to be definitely superior to the other. Outside of a few instances in which sulfapyridine is undoubtedly more effective against the organisms themselves, the choice of one over

the other in any specific infection depends mostly upon the differences in their solubilities and upon the differences in the toxic reactions which they provoke.

Streptococcus Infections.—Experiences with sulfanilamide in the control of infections due to the hemolytic streptococcus have generally been most gratifying, infections in tissues which possess naturally a high degree of immunity or resistance, such as the skin, upper respiratory tract, and urinary tract, generally yielding more rapidly and with smaller amounts of the drug than infections in less resistant tissues such as the central nervous system, lungs, pleura, and abdominal viscera. On the other hand, infections with other types of streptococci have generally not yielded well to sulfanilamide therapy, particularly *Streptococcus viridans* endocarditis and anerobic streptococcus infections. Our impression at this time is that sulfapyridine is as effective as sulfanilamide in acute hemolytic streptococcus infections and more so in *Streptococcus viridans* endocarditis.

We have treated cases of erysipelas and even hemolytic streptococcus meningitis with sulfapyridine alone and have had results which were quite comparable to those commonly observed with sulfanilamide. Despite this, in any *known* hemolytic streptococcus infection, sulfanilamide would seem to be the drug of choice for three reasons: Sulfapyridine causes nausea and vomiting more regularly and more severely, and in the ordinary hemolytic streptococcus infection of the upper respiratory tract or skin this is sufficient to make it less satisfactory. In urinary tract infections, in which a great part of the effectiveness of the drug depends upon its concentration in the free form in the urine, sulfanilamide has the advantage that it is more regularly and more completely excreted into the urine and with a larger and more constant proportion in the free form. Finally, it has been definitely established that the spinal fluid concentration of sulfanilamide is greater in relation to the blood concentration than is the sulfapyridine concentration, so that in cases of hemolytic streptococcus meningitis sulfanilamide again would be superior. An additional advantage of sulfanilamide over sulfapyridine in infections due to this organism or to any other organisms against which the drugs seem to be equally effective is the greater ease with which sulfanilamide can be given parenterally. Sulfanilamide, therefore, does seem to be the drug of choice in infections due to *Streptococcus hemolyticus.*

The effectiveness of either of the drugs against *Streptococcus viridans*, in subacute bacterial endocarditis infections, appears to vary greatly, and some beneficial effects have been reported with sulfanilamide. In our experience, however, sulfanilamide has apparently had no effect upon the course of this disease, even in tremendous dosages (blood concentrations over 50 mg. per cent). Since we have seen definite beneficial effects with the use of sulfapyridine, we should certainly consider it to be first choice in such infections, even though it may, initially, provoke rather severe nausea and vomiting. It should be mentioned here that there is a tendency for the nausea and vomiting which occur at the beginning of sulfapyridine therapy to decrease as time goes on, even when the drug administration is continued.

In general, it is our impression that other strains of streptococci, particularly anerobic strains presumably of intestinal origin, respond poorly to either sulfanilamide or sulfapyridine. The occasional favorable response to sulfapyridine of cases of peritonitis due to *B. coli* and anerobic streptococci suggest its continued trial until further data may establish its real value.

Meningococcic Infections.—The meningococcus is similar to the hemolytic streptococcus in its susceptibility to the two drugs, in that they seem to be equally effective. We have treated cases of meningococcic meningitis with sulfapyridine alone with the same dramatic response that we are accustomed to see with sulfanilamide. The factors mentioned above, however, concerning its slower and less complete diffusion into the spinal fluid make it inferior to sulfanilamide in this infection.

Our present feeling about the treatment of meningococcic meningitis infections is that sulfanilamide therapy with the usual dosage orally, or subcutaneously if necessary, and intrathecal administration for the first day or two is the method of choice. In unusually toxic patients or in patients not definitely improved within 24 to 36 hours, serum therapy should also be employed.

Pneumococcus Infections.—In contrast to the difficulty in differentiating between the effectiveness of sulfanilamide and sulfapyridine in other infections, the superiority of the latter in pneumococcus infections is quite evident. Some success in the treatment of pneumonia was reported with sulfanilamide, particularly with Type III pneumonia, but it was generally felt that the drug was not effective enough to warrant its routine use. During the brief period since sulfapyridine was introduced eighteen months ago, there has been ample evidence that it is an effective therapeutic agent in the treatment of pneumococcic pneumonia. In regard to pneumococcic empyema, it is our feeling that the drug should certainly be used; that it should be continued for a prolonged time; and that, in conjunction, effective methods of drainage should be instituted. The excellent results obtained in cases of pneumococcic meningitis have entirely changed the outlook in this disease, and no less dramatic are the results to be seen in cases of pneumococcic peritonitis. In these last two infections, particularly, advantage may be taken of the solubility of the sodium salt of sulfapyridine for either rectal or intravenous administration.

It might be well to digress at this point to consider a very practical problem which arises in considering the choice between these two drugs. Particularly in children, one is often confronted with a type of infection in which the offending organism is not readily or immediately recognizable. This may happen in cases of otitis media, upper and lower respiratory infections, and, of most importance, in meningitis, where it is particularly important not to delay drug therapy. It is our practice in such cases to choose sulfapyridine as the starting drug since it is effective against a greater variety of organisms. Should the infection then prove to be due to an organism against which sulfanilamide is more useful the drugs may be readily changed.

Gonococcic Infections.—We have had practically no experience in the use of these drugs in gonococcus infections, but their value in such infections is universally accepted, and it is the opinion of those who have had experience with the use of both drugs that sulfapyridine is definitely superior to sulfanilamide in gonococcic infections.

Staphylococcic Infections.—Experimentally, sulfapyridine has been shown to be more effective against the staphylococcus than is sulfanilamide, and clinical trial seems to confirm this. That sulfanilamide has any definite beneficial effect in staphylococcus infections has never been satisfactorily demonstrated except in infections of the urinary tract. We have treated several acute staphylococcus infections with sulfapyridine with what appeared to be very satisfactory results. Despite the rapid improvement of these patients, the true evaluation of the effectiveness of the drug in infections due to this organism must, it seems, be based upon the treatment of the more chronic infections.

Colon Bacillus Infections.—The effectiveness of chemotherapy in the treatment of infections due to this organism is most easily studied in infections of the urinary tract, in which the effectiveness of sulfanilamide is well established. Although in the few cases of colon bacillus pyelitis in which we have used sulfapyridine we have found it quite as effective as sulfanilamide, sulfanilamide would seem to be preferred because, as mentioned before, of the frequent necessity for parenteral administration of the drug; because sulfanilamide is more

regularly and more completely excreted into the urine and with a larger and more constant proportion in the free form; and finally because the medication may have to be continued over a long period of time.

For the various reasons mentioned, we may say then that at the present time sulfanilamide seems to be the drug of choice in all hemolytic streptococcic infections, meningococcic meningitis, and colon bacillus pyelitis. Sulfapyridine, on the other hand, is definitely of greater value in all pneumococcic infections and appears to be more effective than sulfanilamide in infections due to *Streptococcus viridans*, the gonococcus, and the staphylococcus.

News and Notes

Dr. DeWitt Halsey Sherman of Buffalo, N. Y., died on February 1, 1940. Dr. Sherman was a founder of the American Academy of Pediatrics, and also he was vice-president of the American Pediatric Society for 1938-1939.

The **Society for Research in Child Development** will hold its biennial session in Boston on November 8 and 9, 1940.

The meeting of Region III in Kansas City will be held May 16-*18* instead of May 16 and 17 as heretofore announced in the JOURNAL.

Book Reviews

Your Child's Food. Miriam E. Lowenberg, New York. Whittlesy House, 1939. 299 pp. Price $2.50.

The author, who is assistant professor of foods, nutrition and child development, Iowa State College, has compiled an excellent selection of menus and recipes for meals for young children, based on the experience of the nursery school at the college. Part of the book is given over to a discussion in elementary language of food habits, environment at meal time, allergy, etc. Outside of nursery school use, it is perhaps most valuable for unimaginative mothers of the better economic levels.

Virus and Rickettsial Diseases, With Especial Consideration of Their Public Health Significance. A Symposium Held at the Harvard School of Public Health, June 12-17, 1939. Cambridge, Mass., 1940, Harvard University Press, 907 pages. Price $6.50.

This volume consists of thirty articles on viruses and four on rickettsial disease by different members of the staff of the school. In almost every instance the author of the essay has conducted personal investigation in the field and is competent to appraise critically the theories and facts presented. While no effort is made to include all known viruses, the papers discuss most of the more important ones in human and animal pathology. They deal not only with such general subjects as the epidemiologic problems of virus infections, the immunology of virus diseases, and insect vectors, which are discussed clearly and in some detail, but many of the essays concern the clinical and experimental observations on individual virus infections, such as smallpox, vaccinia, measles, mumps, dengue, yellow fever, lymphogranuloma inguinale, influenza, distemper, psittacosis, the central nervous system virus diseases, such as equine encephalitis, poliomyelitis, rabies, lymphatic choriomeningitis, louping ill, and the rickettsial group. An adequate bibliography accompanies each article.

No group of communicable diseases exceeds in economic importance, hygienic significance, or severity the infections caused by filtrable viruses, and, as stated by Zinsser in the introduction, the field of viruses now holds a place in medicine as important as bacteriology itself. The developments and activity of investigators during the past fifteen years in virus study is not appreciated generally, since the rapid accumulation of journal literature has not been made available in any recent similar volume. While the material presented is of much value to laboratory workers on infectious diseases, clinicians and especially pediatricians will find the clearly written and accurate essays not only of considerable interest but of practical worth. It is becoming increasingly evident that the proper care of clinical infectious disease requires a knowledge of the fundamental characteristics and behavior of the infectious agent. In so far as viruses are concerned, most clinicians would profit greatly from this volume, especially the excellent chapters on epidemiology and immunology.

J. V. C.